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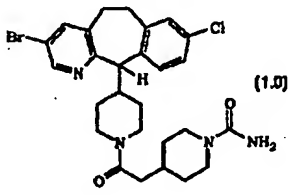
(54) Title: TRICYCLIC AMIDES USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract

Novel compounds, such as formulae (1.0), (4.0), (22.0), (27.0), (32.0) and (39.0) are disclosed. Also disclosed are methods for inhibiting the abnormal growth of cells, for inhibiting famesyl protein transferase and for treating cancers using the novel compounds.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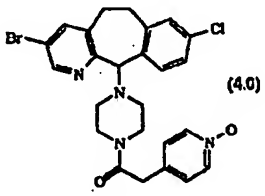
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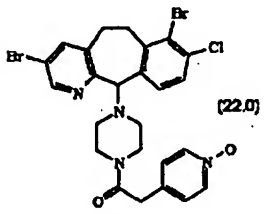
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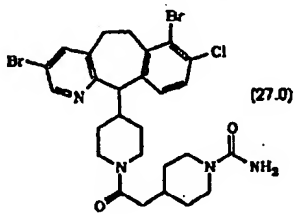
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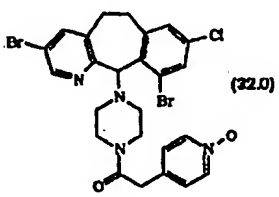
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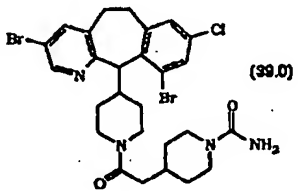
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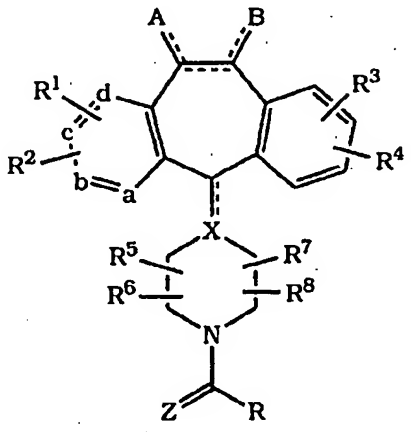
TRICYCLIC AMIDES USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

BACKGROUND

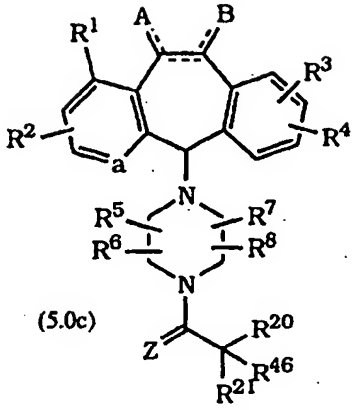
The biological significance of the Ras oncogene, and the role of both Ras and the enzyme known as farnesyl protein transferase in the conversion of normal cells to cancer cells, are described in PCT International Publication Nos. WO95/00497 and WO95/10516. Each of those publications also describes a distinct class of compounds which inhibit the activity of the enzyme farnesyl protein transferase, and thereby the farnesylation of the Ras protein.

PCT International Publication No. WO95/10516 relates to tricyclic amide and urea compounds of the general formula (1.0)



(1.0)

and their use in a method for inhibiting Ras function and the abnormal growth of cells. A number of sub-generic classes of compounds of formula (1.0) are described, which include compounds of the formulae (5.0c), (5.1c) and (5.2a)



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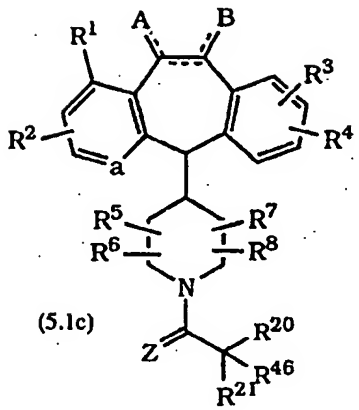
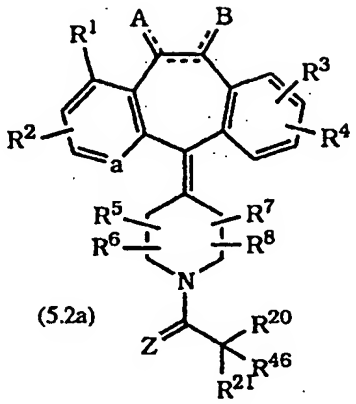


(5.1c)

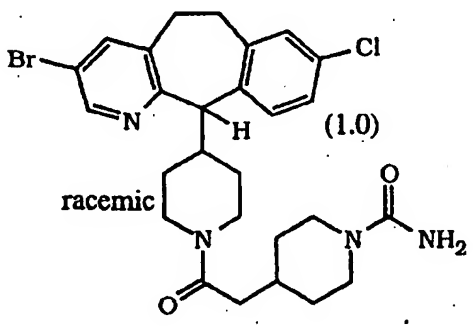


(5.2a)

as well as the 11-R-isomer and 11-S-isomers of compounds (5.0c) and (5.1c). A number of specific compounds within each such sub-genus are also described therein, as is the biological activity of those compounds.

SUMMARY OF THE INVENTION

The present invention provides novel tricyclic amide compounds selected from the group consisting of:



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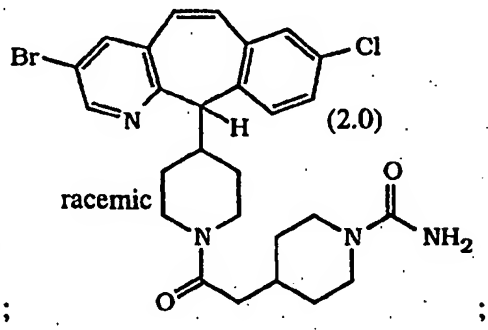

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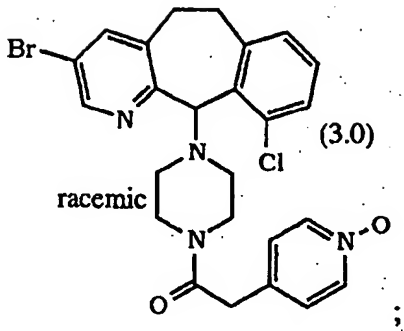
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N
Cl
(3.0)
racemic
N
N
O
O

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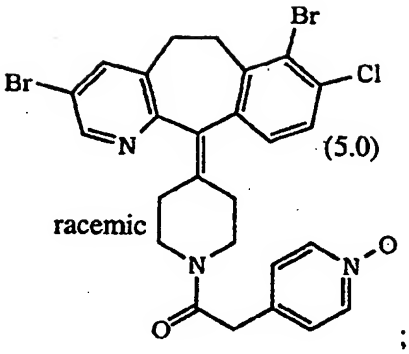
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Cl
N
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N
O
O

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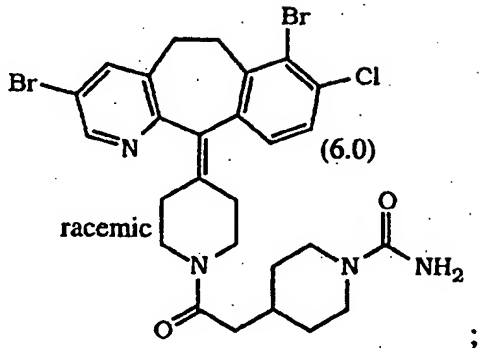
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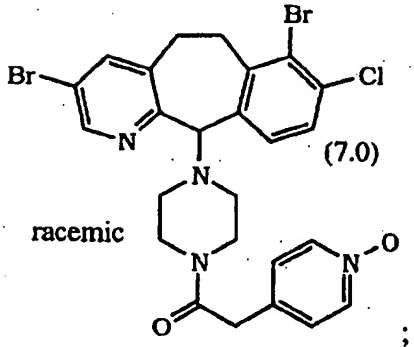
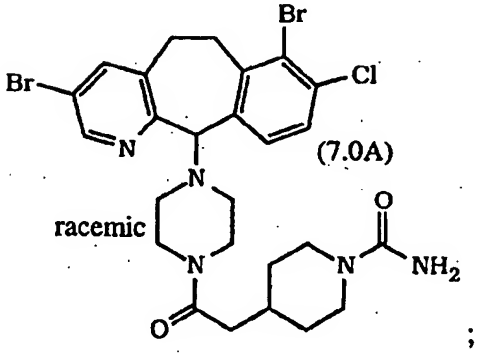
NH2
N
O

;

5


Br
Br
Cl
N
(7.0)
racemic
N
N
O
O

;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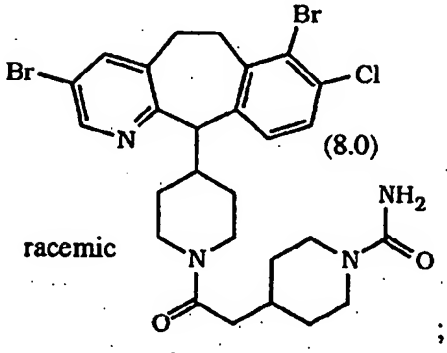
Br
Cl
N
(7.0A)
racemic
N
O
N
NH2
O

;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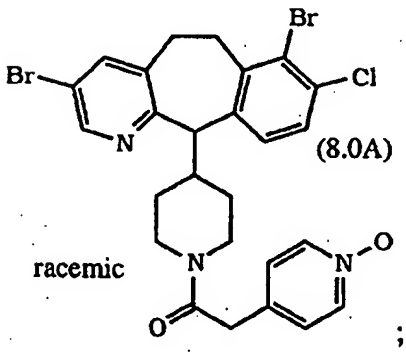
Br
Cl
N
(8.0)
racemic
NH2
N
N
O
O

;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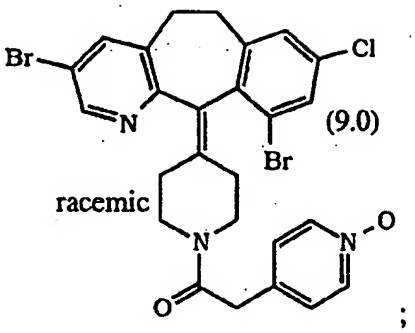
Br
Cl
N
(8.0A)
racemic
N
N
O
O

;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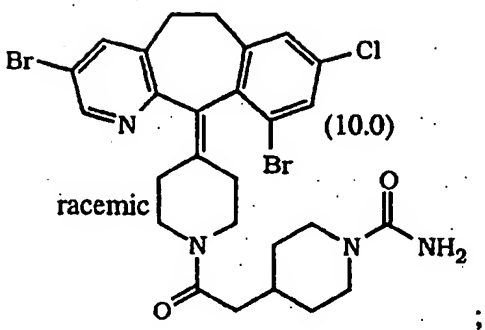
Cl
(9.0)
Br
racemic
N
O
N
O
;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Cl
(10.0)
Br
racemic
O
NH2
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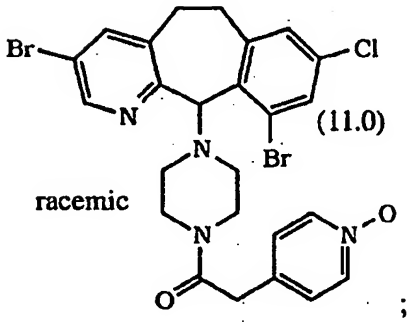
N
O
;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N
O
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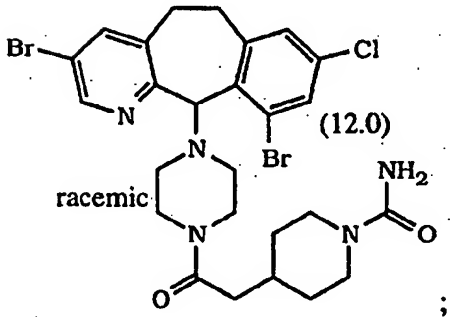
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Br
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N
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O
O
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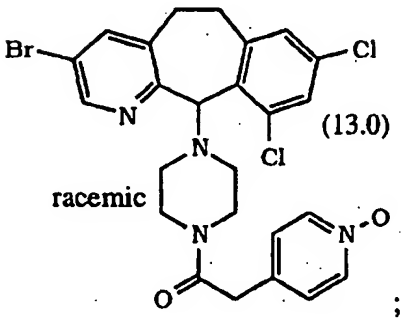
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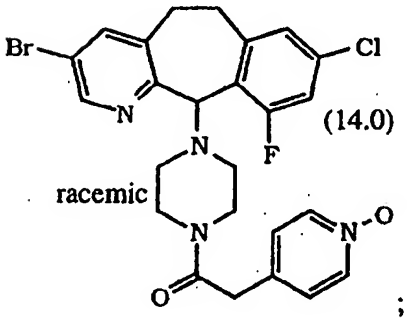
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Cl
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F
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N
O
O
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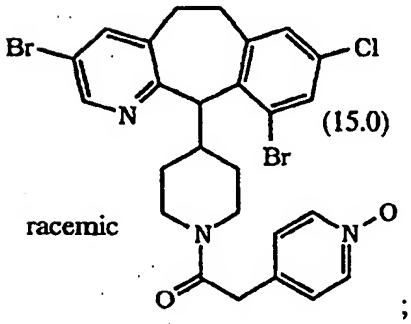
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Br
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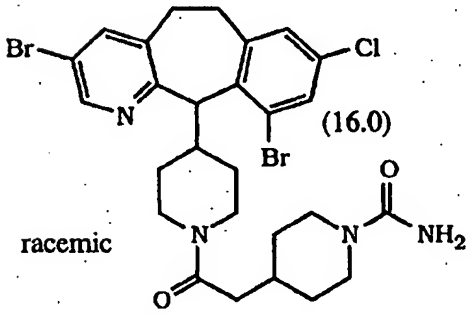
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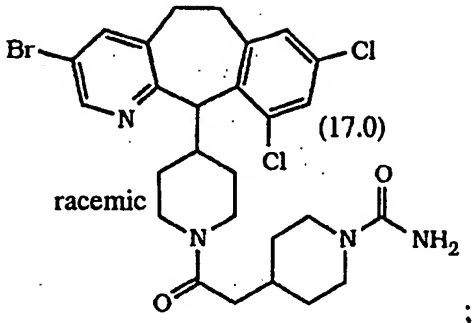

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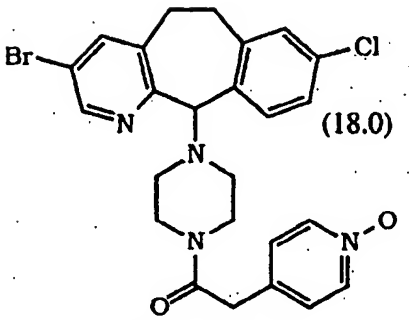

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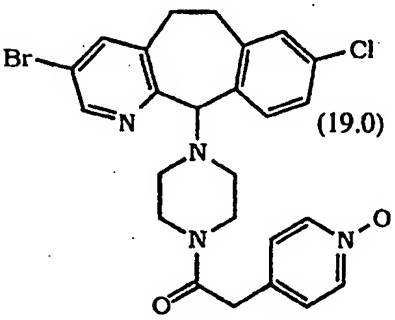

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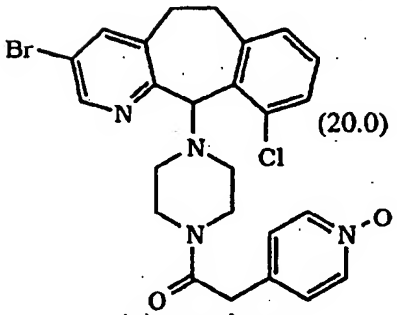

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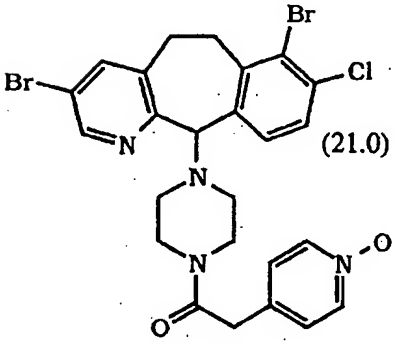

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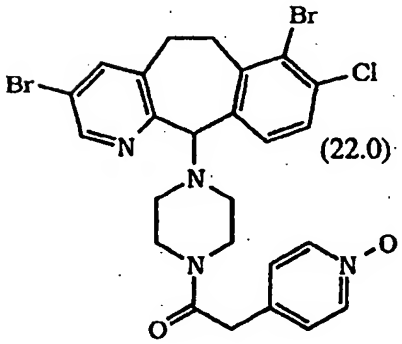

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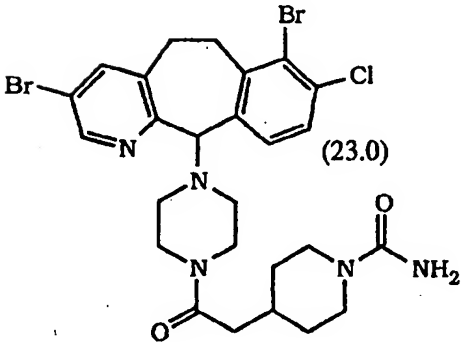

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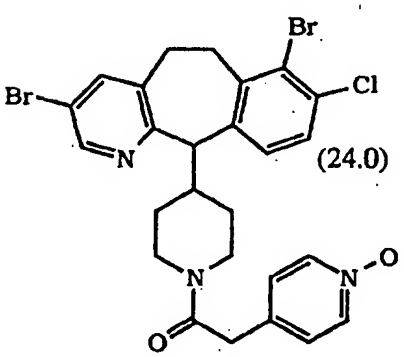

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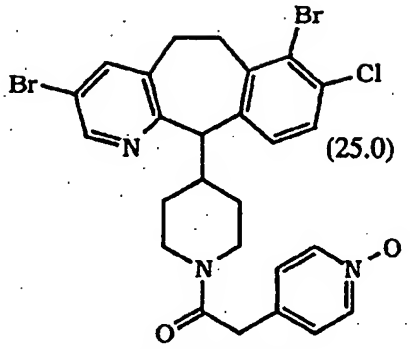

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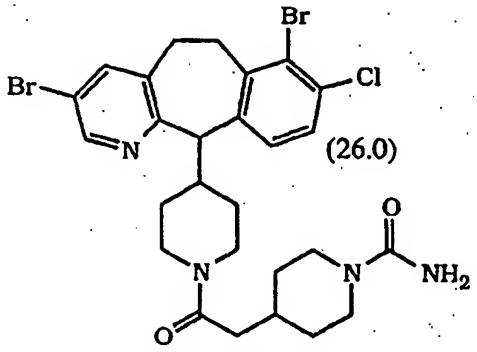

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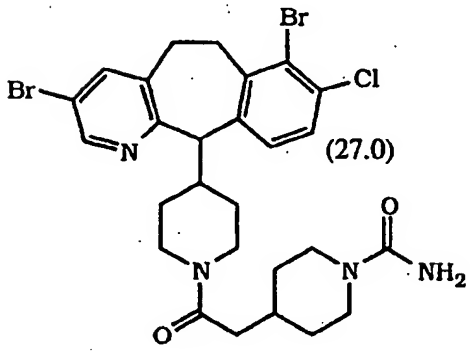

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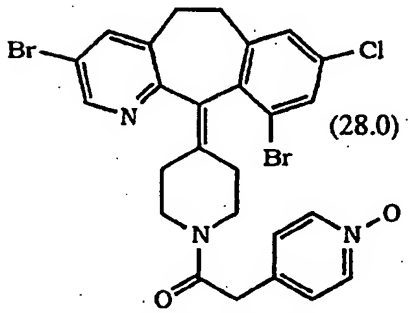

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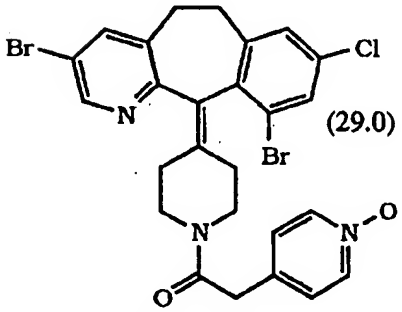

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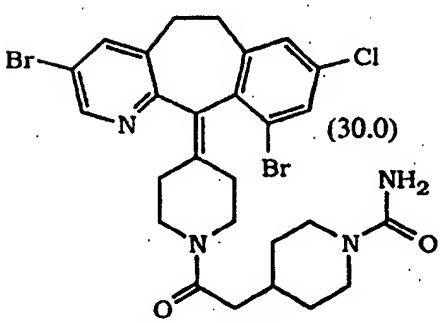

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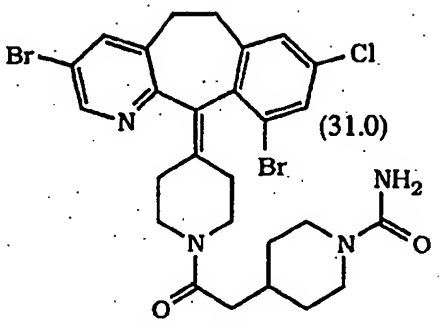
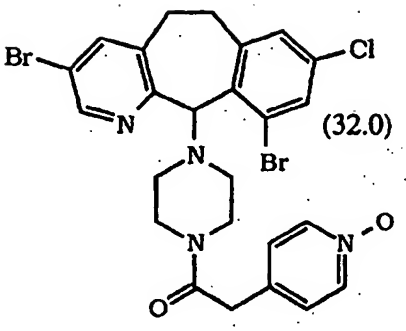
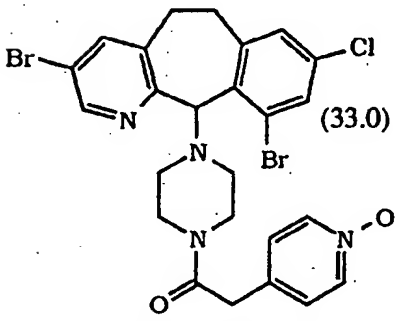


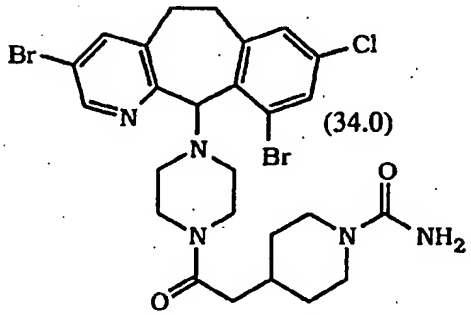
(+)-enantiomer ;



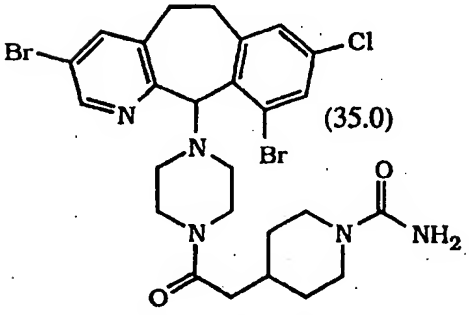
(+) - enantiomer ;



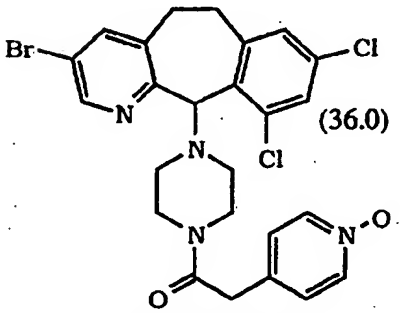
(-) - enantiomer ;



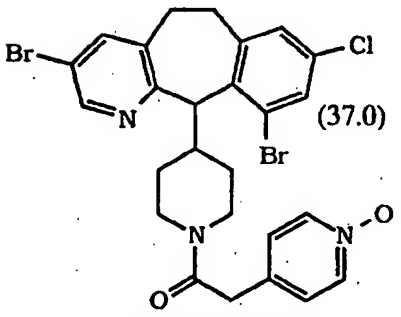
(+) - enantiomer ;



(-) - enantiomer ;



(+)-enantiomer ;



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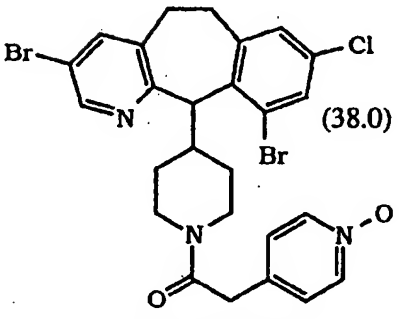

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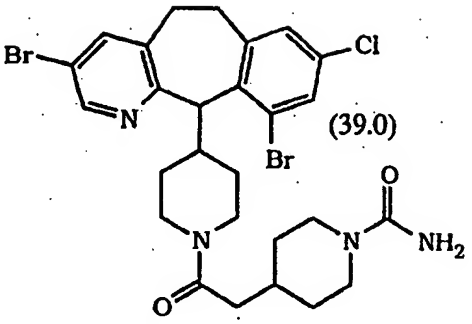
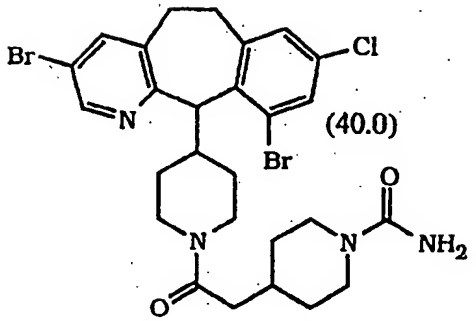
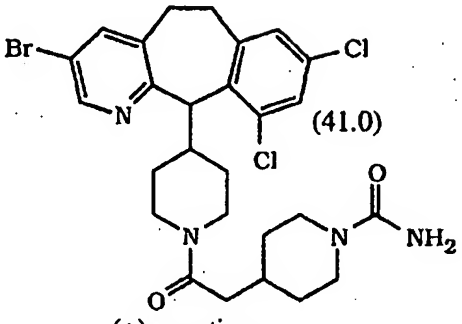


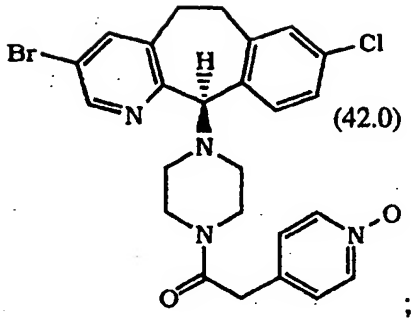
(+) - enantiomer ;



(-) - enantiomer ;



(+)-enantiomer ;



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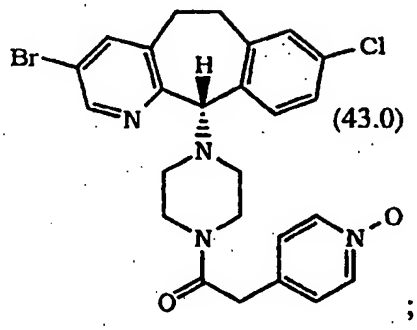

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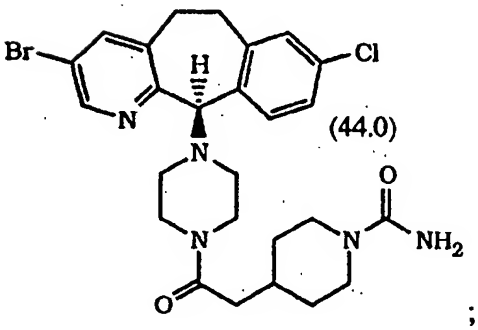

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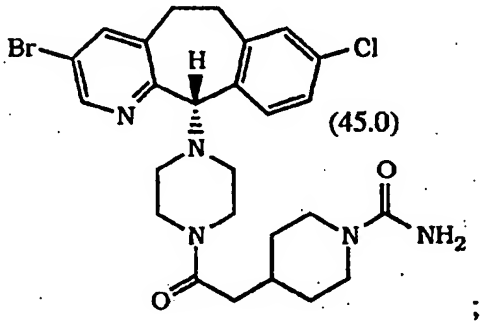

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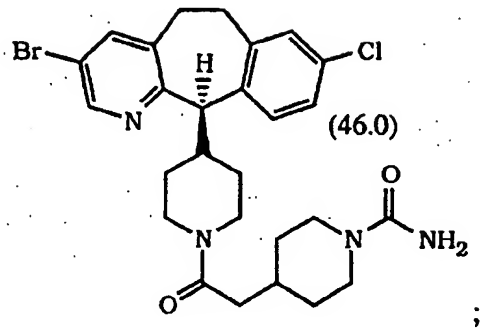
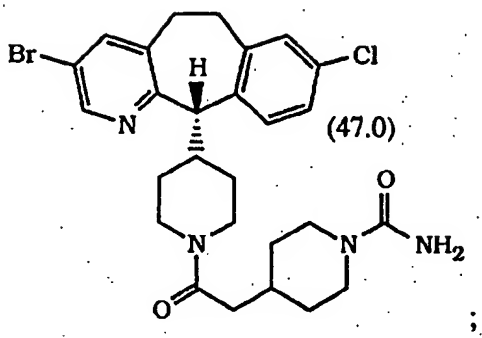

(46.0)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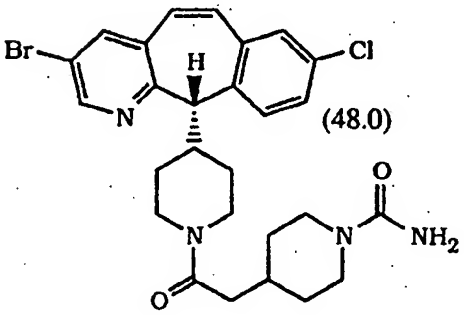
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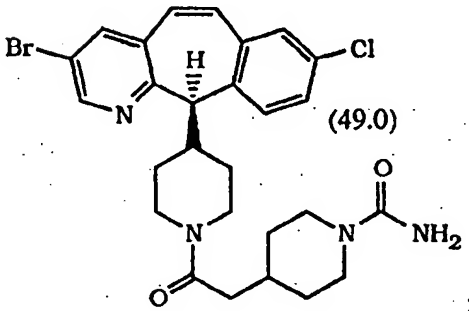
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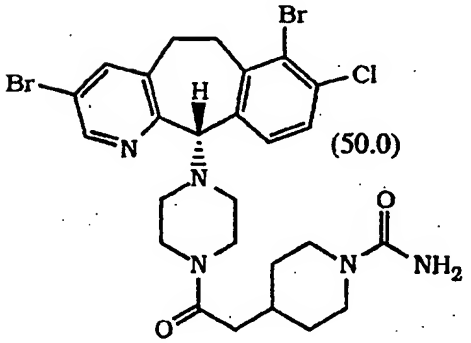
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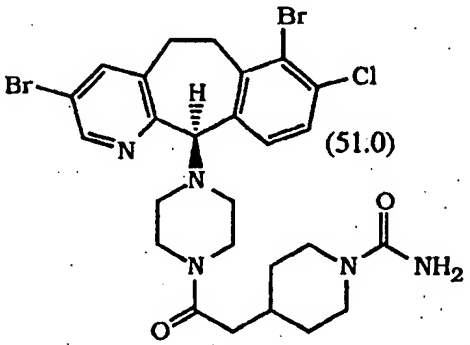
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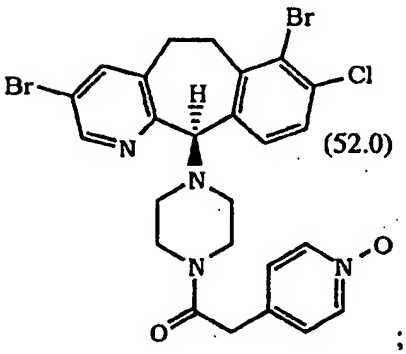
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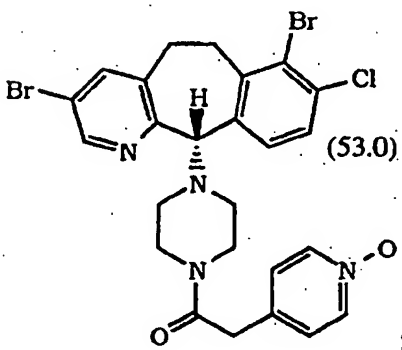
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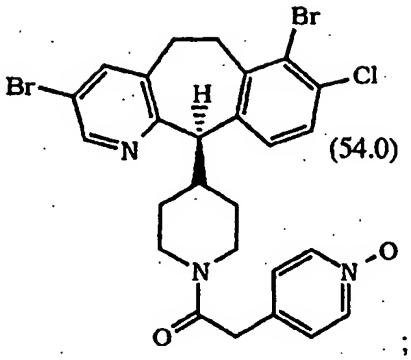
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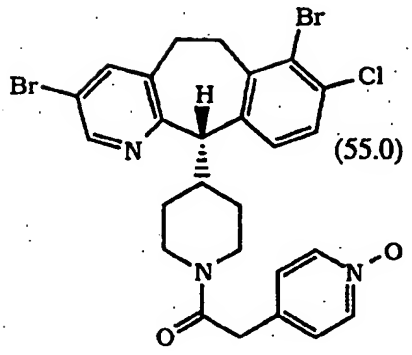
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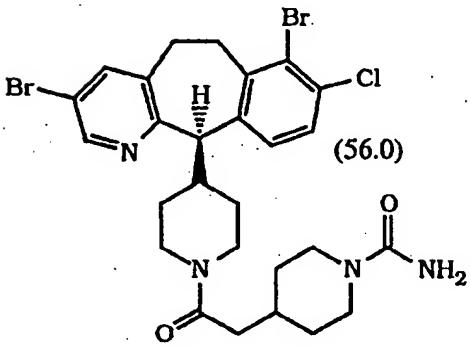
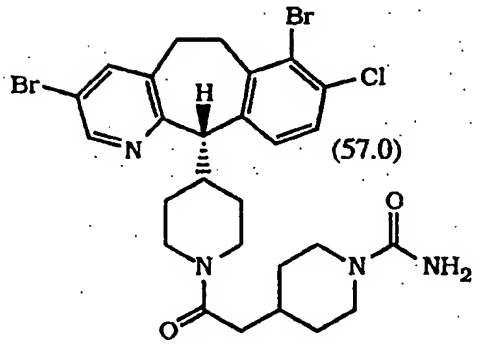
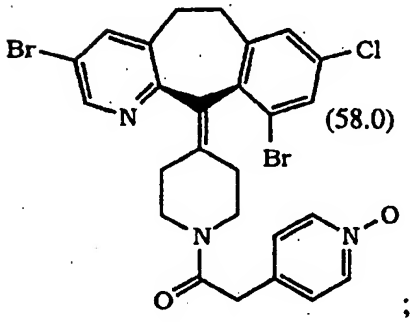

(56.0) ;


(57.0) ;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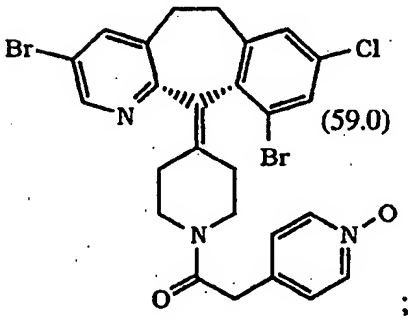
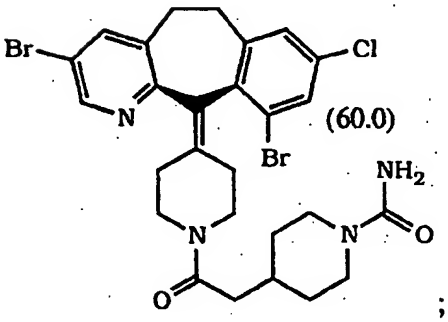

(59.0) ;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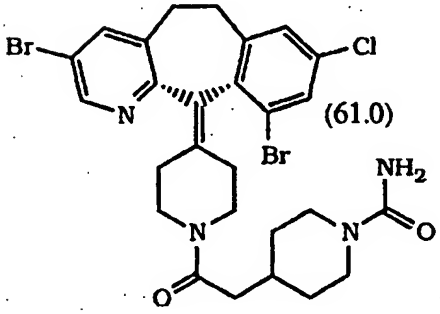
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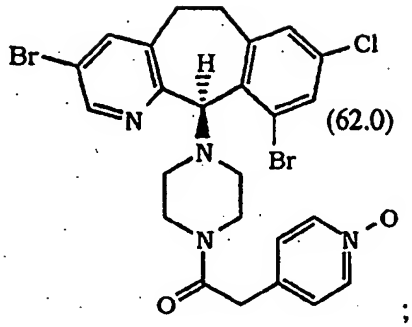
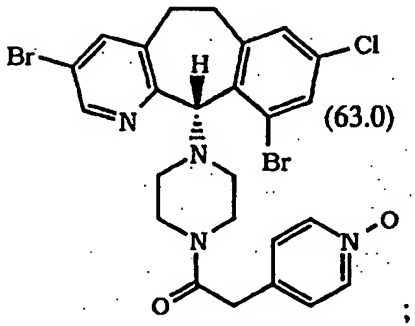
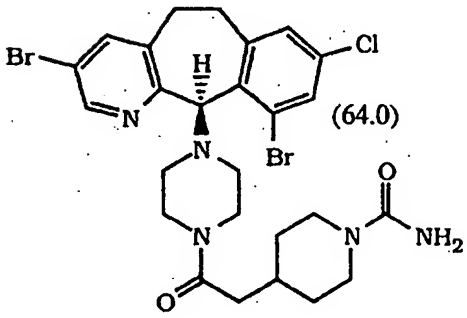
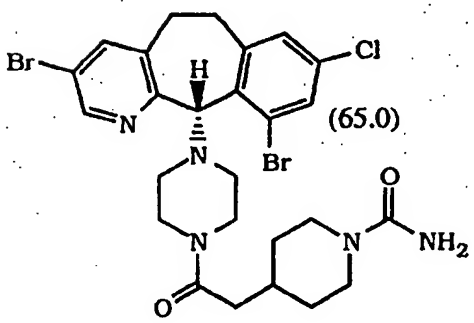

(62.0) ;


(63.0) ;


(64.0) ;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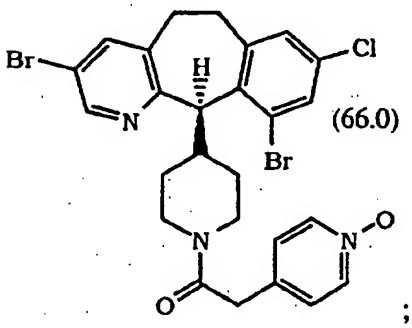
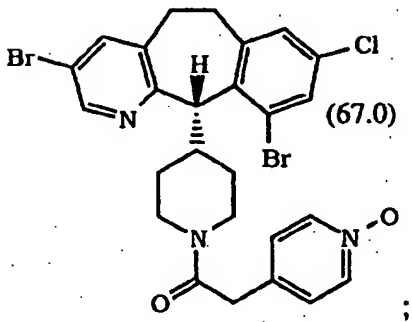

(66.0) ;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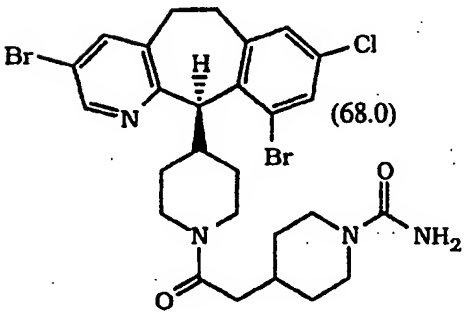
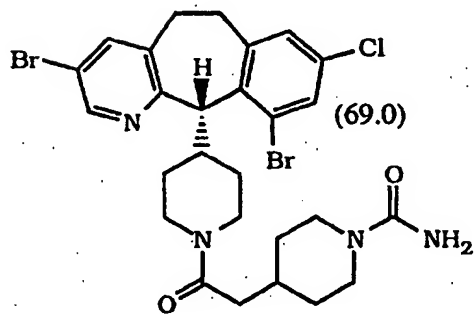
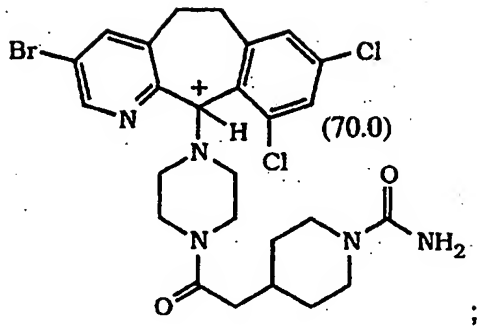
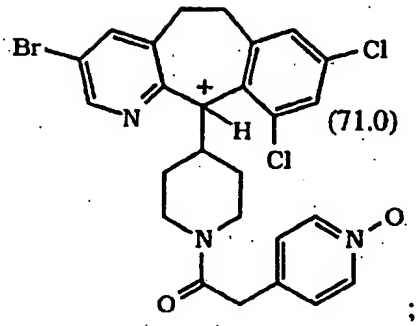
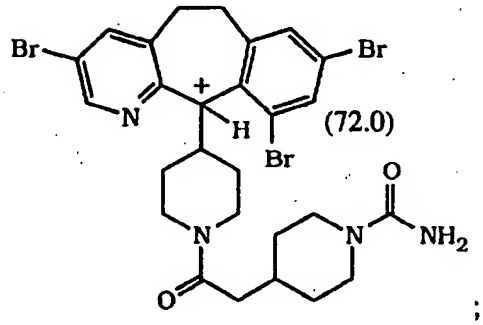
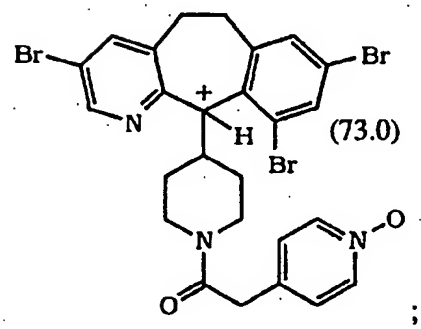

(68.0) ;

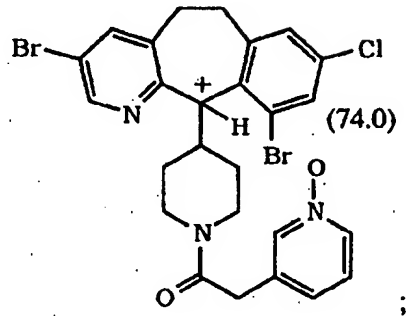

(69.0) ;

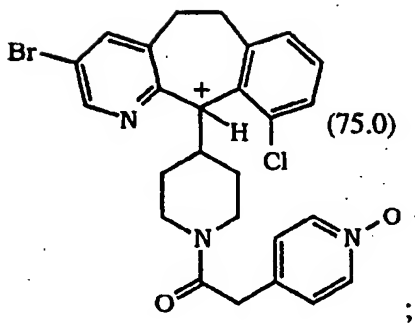

(70.0) ;


(71.0) ;


(72.0) ;


(73.0) ;


(74.0) ;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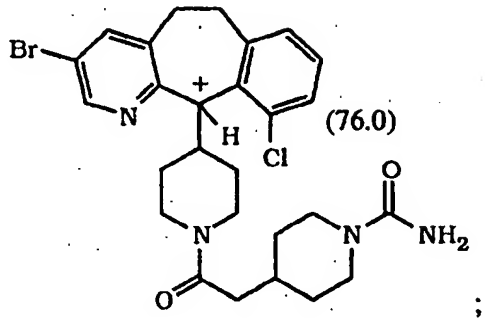
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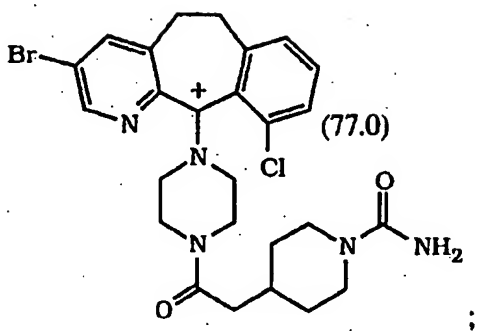

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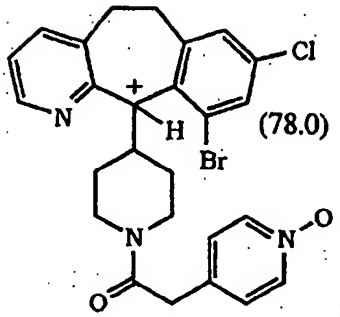

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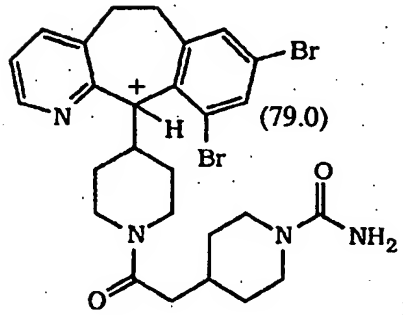

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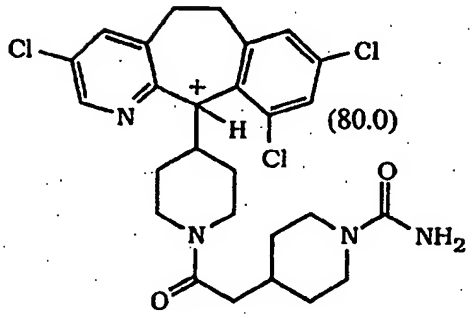


or pharmaceutically acceptable salts thereof.

Optical rotation of the compounds ((+)- or (-)-) are measured in methanol or ethanol at 25°C.

This invention includes the above compounds in the amorphous state or in the cyrstalline state.

Thus, compounds of this invention include compounds selected from the group consisting of: Compounds 1.0, 2.0, 3.0, 5.0, 6.0, 7.0, 7.0A, 8.0, 8.0A, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, and 17.0, or pharmaceutically acceptable salts thereof, wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: Compounds 18.0, 19.0, 20.0, 21.0, 22.0, 23.0, 24.0, 25.0, 26.0, 27.0, 28.0, 29.0, 30.0, 31.0, 32.0, 33.0, 34.0, 35.0, 36.0, 37.0, 38.0, 39.0, 40.0, and 41.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

Compounds of this invention also include compounds selected from the group consisting of: (+)-enantiomer Compounds 70.0, 71.0, 72.0, 73.0, 74.0, 75.0, 76.0, 77.0, 78.0, 79.0 and 80.0, or pharmaceutically acceptable salts thereof, and wherein said compounds are as defined above.

Also, compounds of this invention include compounds selected from the group consisting of: Compounds 42.0, 43.0, 44.0, 45.0, 46.0, 47.0, 48.0, 49.0, 50.0, 51.0, 52.0, 53.0, 54.0, 55.0, 56.0, 57.0, 58.0, 59.0, 60.0, 61.0, 62.0, 63.0, 64.0, 65.0, 66.0, 67.0, 68.0 and 69.0, or pharmaceutically acceptable salts thereof, wherein said compounds are as defined above.

Preferred compounds include the 3,7,8-trihalo compounds having a (-)-optical rotation. For example, Compounds 22.0, 23.0, 25.0 and 27.0.

Preferred compounds also include the 3,8,10-trihalo compounds having a (+)-optical rotation. For example, Compounds 29.0, 31.0, 32.0, 34.0, 36.0, 37.0, 39.0 and 41.0.

Preferred compounds also include the 3,10-dihalo compounds having a (+)-optical rotation. for example, Compound 20.0.

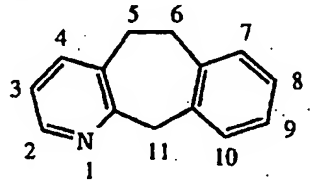
Preferred compounds also include the 3,7-dibromo-8-chloro compounds having S stereochemistry at the C-11 position. For example, Compounds 50.0, 53.0, 55.0 and 57.0.

Preferred compounds also include the 3,10-dibromo-8-chlorocompounds having R stereochemistry at the C-11 position. For example, Compounds 62.0, 64.0, 66.0 and 68.0.

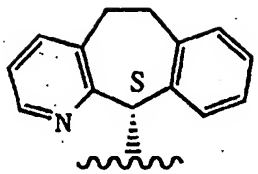
Preferred compounds also include Compounds 16.0, 17.0, 39.0, 40.0, 41.0, 68.0 and 69.0.

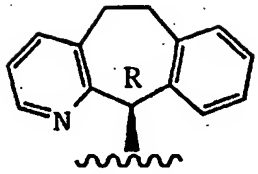
More preferred compounds are Compounds 16.0, 39.0, 40.0, 68.0 and 69.0. Most preferred compounds are Compounds 16.0, 39.0 and 68.0. Even more preferred is Compound 39.0 or 68.0.

Those skilled in the art will appreciate that the tricyclic ring system is numbered:



Those skilled in the art will also appreciate that the S and R stereochemistry at the C-11 bond are:





Inhibition of farnesyl protein transferase by the tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. The compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung

cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, breast cancers and prostate cancers.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein

transferase, and thus show antiproliferative activity against ras transformed cells.

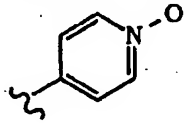
DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

M^+-represents the molecular ion of the molecule in the mass spectrum;

MH^+-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

Pyridyl N-oxides are herein represented by the group



The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxy-benzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); ethyl chloroformate ($ClCO_2Et$); 1-(3-dimethylaminopropyl)-3-ethyl carbodiimde hydrochloride (DEC); diisobutylaluminum hydride (DIBAL); isopropanol (iPrOH); dimethylsulfoxide (DMSO)

Certain compounds of the present invention may exist in different isomeric forms (e.g., enantiomers or diastereoisomers) including atropisomers (i.e., compounds wherein the 7-membered ring is in a fixed conformation such that the 11-carbon atom is positioned above or below the plane of the fused beznene rings due to the presence of a 10-bromo substituent). The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong

acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

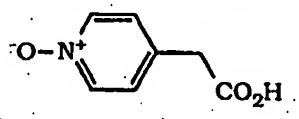
All such salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The compounds of the present invention can be prepared by the procedures described below.

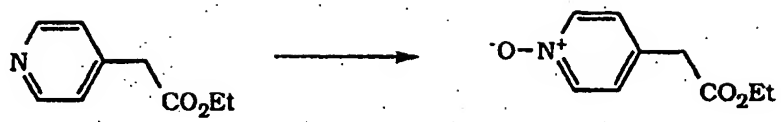
The compound of Example 10 is obtained in the cyrstalline state. Those skilled in the art will appreciate that compounds obtained in the amorphous state can be obtained in the cyrstalline state by cyrstallizing the amorphous materials from solvents or solvent mixtures such as acetone, diethyl ether, ethyl acetate, ethanol, 2-propanol, tert-butyl ether, water and the like according to procedures well known in the art.

Those skilled in the art will also appreciate that the racemic mixture of Compound 7.0A can be made according to the procedures described below. For Example, the intermediate of Preparative Example 6 can be used to prepare Compound 7.0A.

PREPARATIVE EXAMPLE 1



Step A:

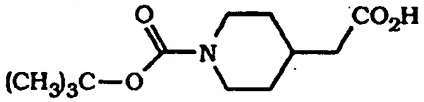


Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous) and then water. Dry over $MgSO_4$, concentrate *in vacuo* to a residue, and chromatograph (silica gel, 2%-5.5% (10% NH_4OH in MeOH)/CH_2Cl_2)to give 8.12 g of the product compound. Mass Spec.: MH^+ = 182.15

Step B:

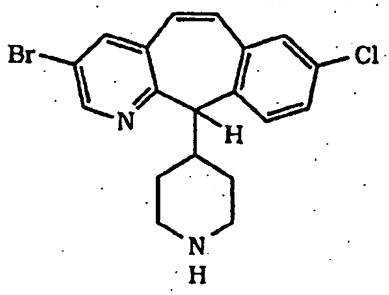
Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate *in vacuo* to a residue. Add 200 mL of dry EtOH, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give 2.43 g of the title compound.

PREPARATIVE EXAMPLE 2

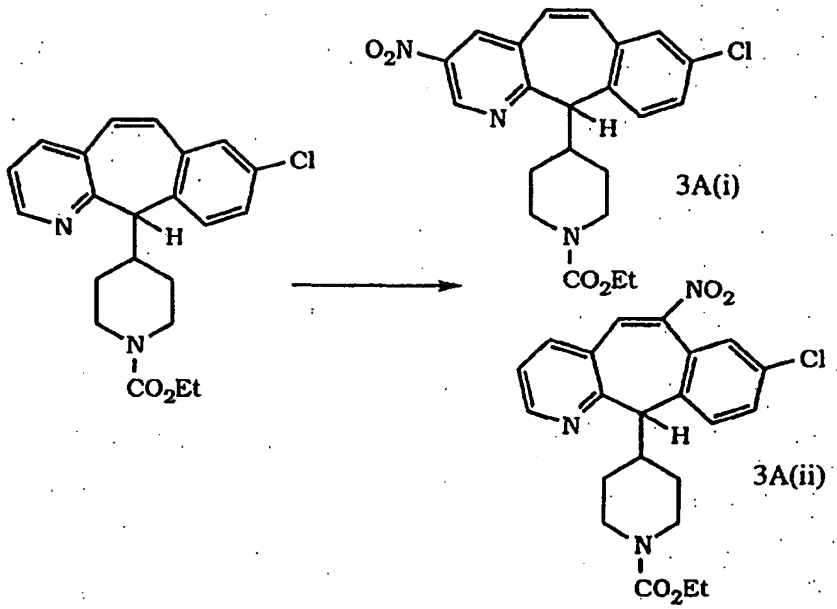


The title compound is prepared via the process disclosed in PCT International Publication No. WO95/10516.

PREPARATIVE EXAMPLE 3



Step A:

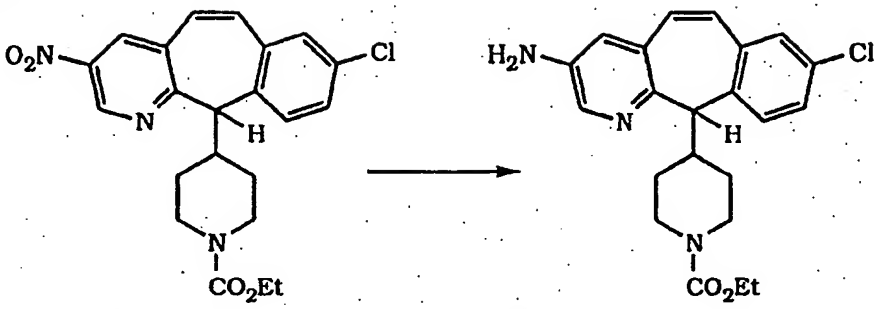


Combine 14.95 g (39 mmol) of 8-chloro-11-(1-ethoxycarbonyl-4-piperidinyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine and 150 mL of CH_2Cl_2, then add 13.07 g (42.9 mmol) of $(nBu)_4NNO_3$ and cool the mixture to 0°C. Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH_2Cl_2 over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated $NaHCO_3$ (aqueous), water and brine. Dry the organic solution over Na_2SO_4, concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds 3A(i) and 3A(ii), respectively.

Mass Spec. for compound 3A(i): MH^+ = 428.2.

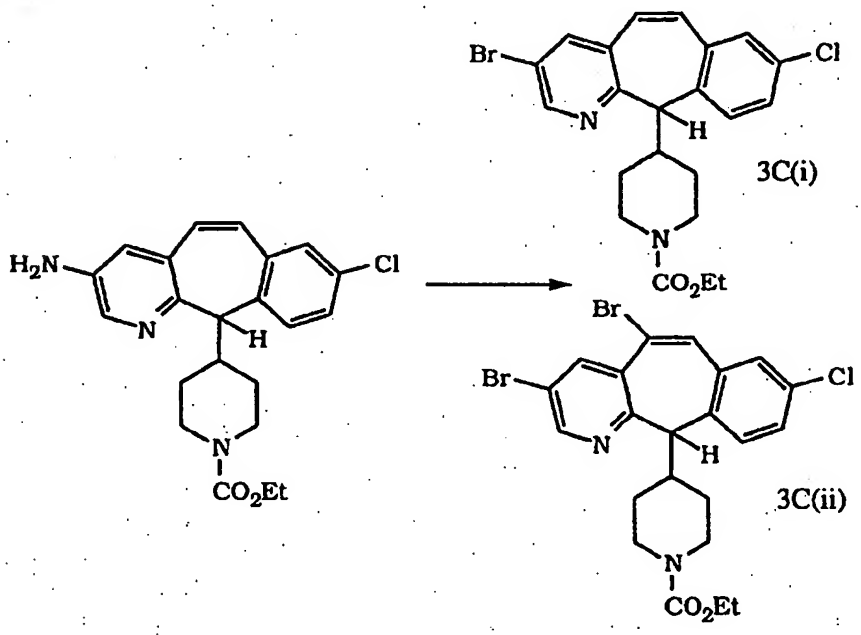
Mass Spec. for compound 3A(ii): MH^+ = 428.3.

Step B:



Combine 22.0 g (51.4 mmol) of the product 3A(i) from Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of $CaCl_2$, and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours more. Filter the hot mixture through celite®, wash the celite® with 50 mL of hot EtOH and concentrate the filtrate *in vacuo* to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, $MeOH/CH_2Cl_2$ gradient) to give 16.47 g of the product compound. MH^+ = 398.

Step C:

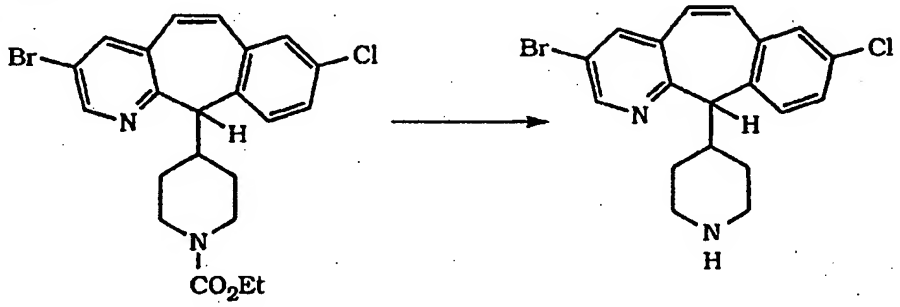


Combine 16.47 g (41.4 mmol) of the product from Step B, and 150 mL of 48% HBr (aqueous) and cool to -3°C. Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of $NaNO_2$ in 85 mL of water. Stir for 45 minutes at -3° to 0°C, then adjust to pH = 10 by adding 50% NaOH (aqueous). Extract with EtOAc, wash the extracts with brine and dry the extracts over Na_2SO_4. Concentrate to a residue and chromatograph (silica gel, EtOAc/hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 3C(i) and 3C(ii), respectively.

Mass Spec. for compound 3C(i): MH^+ = 461.2.

Mass Spec. for compound 3C(ii): MH^+ = 539.

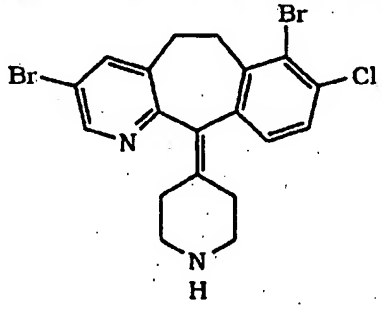
Step D:



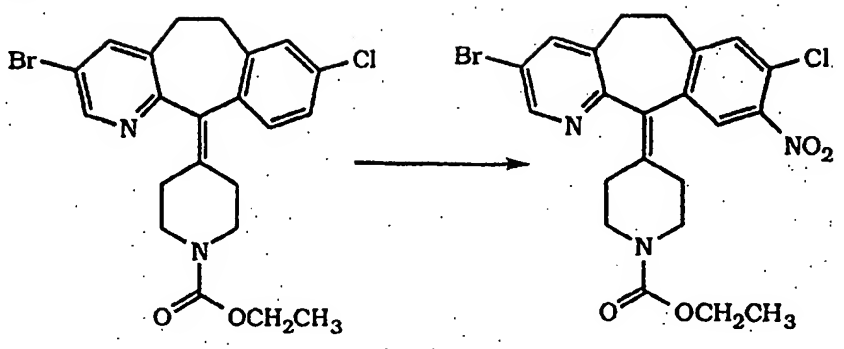
Hydrolyze the product 3C(i) of Step C by dissolving in concentrated HCl and heating to about 100°C for 16 hours. Cool the mixture, then neutralize with 1 M NaOH (aqueous). Extract with CH_2Cl_2, dry the extracts over $MgSO_4$, filter and concentrate *in vacuo* to the title compound.

Mass Spec.: MH^+ = 466.9.

PREPARATIVE EXAMPLE 4

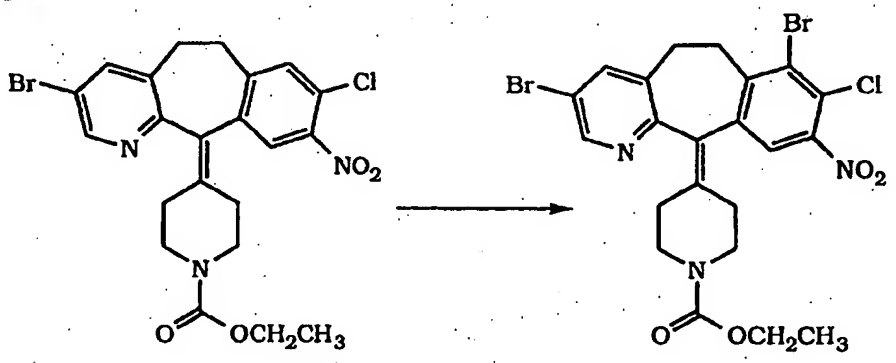


Step A:



Combine 25.86 g (55.9 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 250 mL of concentrated H_2SO_4 at -5°C, then add 4.8 g (56.4 mmol) of $NaNO_3$ and stir for 2 hours. Pour the mixture into 600 g of ice and basify with concentrated NH_4OH (aqueous). Filter the mixture, wash with 300 mL of water, then extract with 500 mL of CH_2Cl_2. Wash the extract with 200 mL of water, dry over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10% EtOAc/ CH_2Cl_2) to give 24.4 g (86% yield) of the product. m.p. = 165-167°C, Mass Spec.: MH^+ = 506 (CI). Elemental analysis: calculated - C, 52.13; H, 4.17; N, 8.29
found - C, 52.18; H, 4.51; N, 8.16.

Step B:

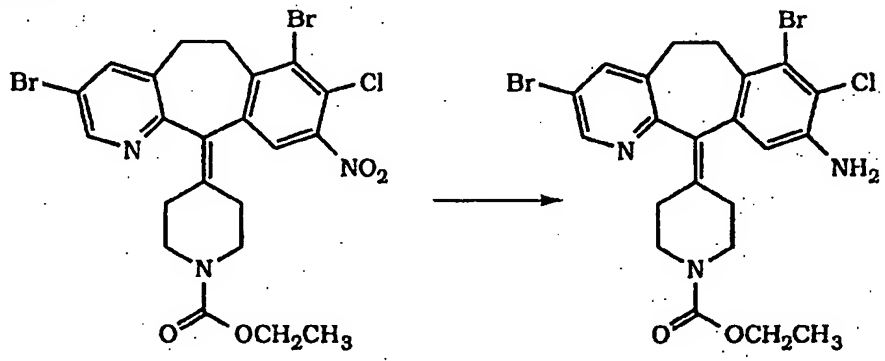


Combine 20 g (40.5 mmol) of the product of Step A and 200 mL of concentrated H_2SO_4 at 20°C, then cool the mixture to 0°C. Add 7.12 g (24.89 mmol) of 1,3-dibromo-5,5-dimethyl-hydantoin to the mixture and stir for 3 hours at 20°C. Cool to 0°C, add an additional 1.0 g (3.5 mmol) of the dibromohydantoin and stir at 20°C for 2 hours. Pour the mixture into 400 g of ice,

basify with concentrated NH_4OH (aqueous) at 0°C, and collect the resulting solid by filtration. Wash the solid with 300 mL of water, slurry in 200 mL of acetone and filter to provide 19.79 g (85.6% yield) of the product. m.p. = 236-237°C, Mass Spec.: MH^+ = 584 (CI).

Elemental analysis: calculated - C, 45.11; H, 3.44; N, 7.17
found - C, 44.95; H, 3.57; N, 7.16.

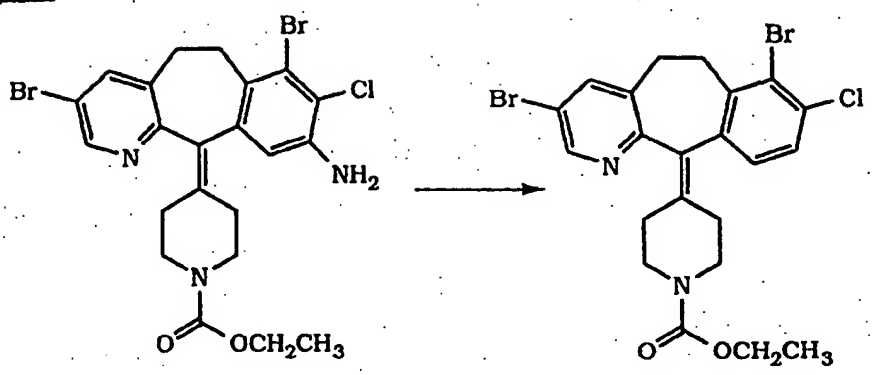
Step C:



Combine 25 g (447 mmol) of Fe filings, 10 g (90 mmol) of $CaCl_2$ and a suspension of 20 g (34.19 mmol) of the product of Step B in 700 mL of 90:10 EtOH/water at 50°C. Heat the mixture at reflux overnight, filter through Celite® and wash the filter cake with 2 X 200 mL of hot EtOH. Combine the filtrate and washes, and concentrate *in vacuo* to a residue. Extract the residue with 600 mL of CH_2Cl_2, wash with 300 mL of water and dry over $MgSO_4$. Filter and concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/CH_2Cl_2) to give 11.4 g (60% yield) of the product. m.p. = 211-212°C,
Mass Spec.: MH^+ = 554 (CI).

Elemental analysis: calculated - C, 47.55; H, 3.99; N, 7.56
found - C, 47.45; H, 4.31; N, 7.49.

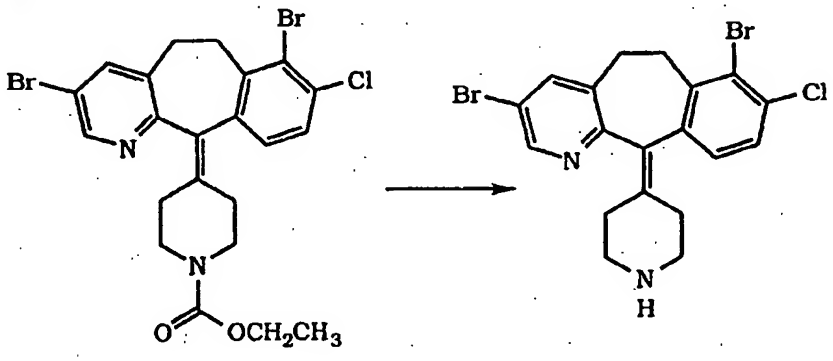
Step D:



Slowly add (in portions) 20 g (35.9 mmol) of the product of Step C to a solution of 8 g (116 mmol) of $NaNO_2$ in 120 mL of concentrated HCl (aqueous) at -10°C. Stir the resulting mixture at 0°C for 2 hours, then slowly add (dropwise) 150 mL (1.44 mole) of 50% H_3PO_2 at 0°C over a 1 hour period. Stir at 0°C for 3 hours, then pour into 600 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 X 300 mL of CH_2Cl_2, dry the extracts over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 25% EtOAc/ hexanes) to give 13.67 g (70% yield) of the product. m.p. = 163-165°C. Mass Spec.: MH^+ = 539 (CI).

Elemental analysis: calculated - C, 48.97; H, 4.05; N, 5.22
found - C, 48.86; H, 3.91; N, 5.18.

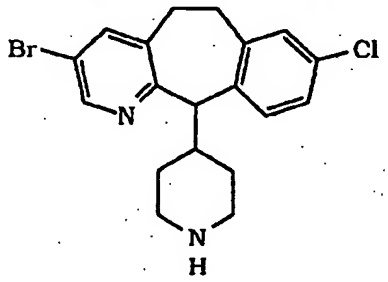
Step E:



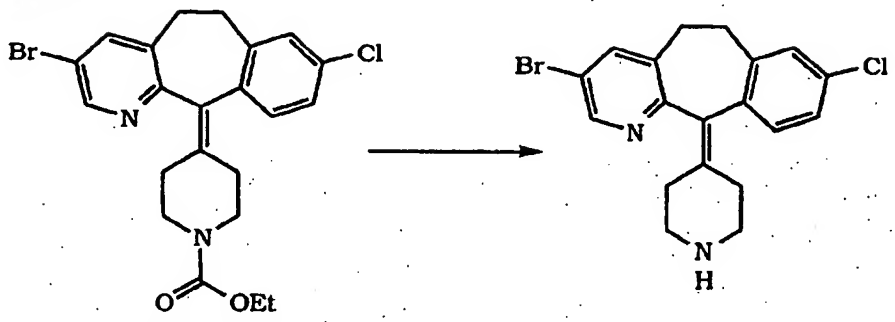
Combine 6.8 g (12.59 mmol) of the product of Step D and 100 mL of concentrated HCl (aqueous) and stir at 85°C overnight. Cool the mixture, pour it into 300 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 x 300 mL of CH_2Cl_2, then dry the extracts over $MgSO_4$. Filter, concentrate *in*

vacuo to a residue, then chromatograph (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aqueous)) to give 5.4 g (92% yield) of the title compound. m.p. = 172-174°C, Mass Spec.: MH^+ = 467. Elemental analysis: calculated - C, 48.69; H, 3.65; N, 5.97 found - C, 48.83; H, 3.80; N, 5.97.

PREPARATIVE EXAMPLE 5

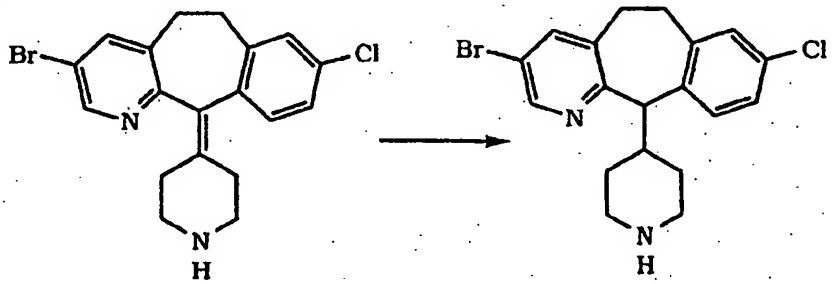


Step A:



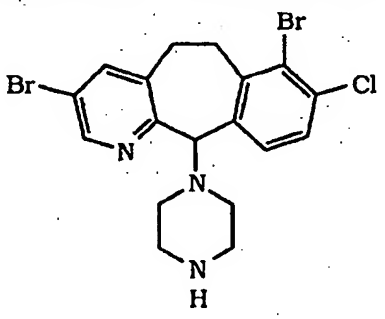
Hydrolyze 2.42 g of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester via substantially the same procedure as described in Preparative Example 3, Step D, to give 1.39 g (69% yield) of the product. MH^+ = 389.

Step B:



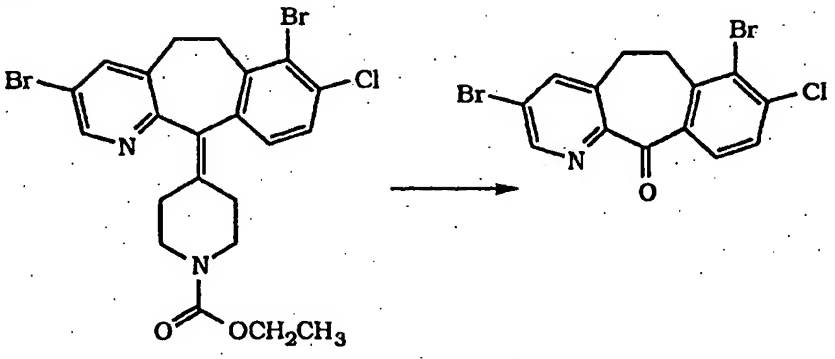
Combine 1 g (2.48 mmol) of the product of Step A and 25 mL of dry toluene, add 2.5 mL of 1 M DIBAL in toluene and heat the mixture at reflux. After 0.5 hours, add another 2.5 mL of 1 M DIBAL in toluene and heat at reflux for 1 hour. (The reaction is monitored by TLC using 50% MeOH/CH_2Cl_2 +NH_4OH (aqueous).) Cool the mixture to room temperature, add 50 mL of 1 N HCl (aqueous) and stir for 5 min. Add 100 mL of 1 N NaOH (aqueous), then extract with EtOAc (3 X 150 mL). Dry the extracts over $MgSO_4$, filter and concentrate *in vacuo* to give 1.1 g of the title compound. MH^+ = 391.

PREPARATIVE EXAMPLE 6



[racemic as well as (+)- and (-)-enantiomers]

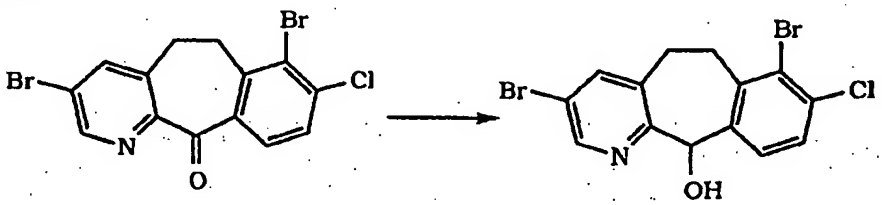
Step A:



Combine 16.6 g (0.03 mole) of the product of Preparative Example 4, Step D, with a 3:1 solution of CH_3CN and water (212.65 mL CH_3CN and 70.8 mL of water) and stir the resulting slurry overnight at room temperature. Add 32.833 g (0.153 mole) of $NaIO_4$ and then 0.31 g (2.30 mmol) of RuO_2 and stir at room temperature (the addition of RuO_2 is accompanied by an exothermic reaction and the temperature climbs from 20° to

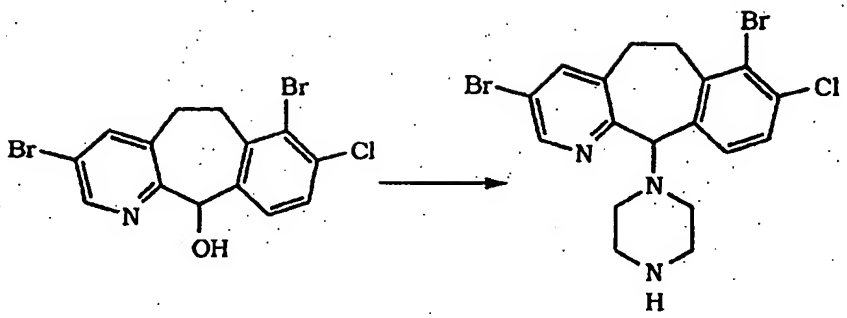
30°C). Stir the mixture for 1.3 hrs. (temperature returned to 25°C after about 30 min.), then filter to remove the solids and wash the solids with CH_2Cl_2. Concentrate the filtrate *in vacuo* to a residue and dissolve the residue in CH_2Cl_2. Filter to remove insoluble solids and wash the solids with CH_2Cl_2. Wash the filtrate with water, concentrate to a volume of about 200 mL and wash with bleach, then with water. Extract with 6 N HCl (aqueous). Cool the aqueous extract to 0°C and slowly add 50% NaOH (aqueous) to adjust to pH = 4 while keeping the temperature <30°C. Extract twice with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Slurry the residue in 20 mL of EtOH and cool to 0°C. Collect the resulting solids by filtration and dry the solids *in vacuo* to give 7.95 g of the product. ^1H NMR ($CDCl_3$, 200 MHz): 8.7 (s, 1H); 7.85 (m, 6H); 7.5 (d, 2H); 3.45 (m, 2H); 3.15 (m, 2H).

Step B:



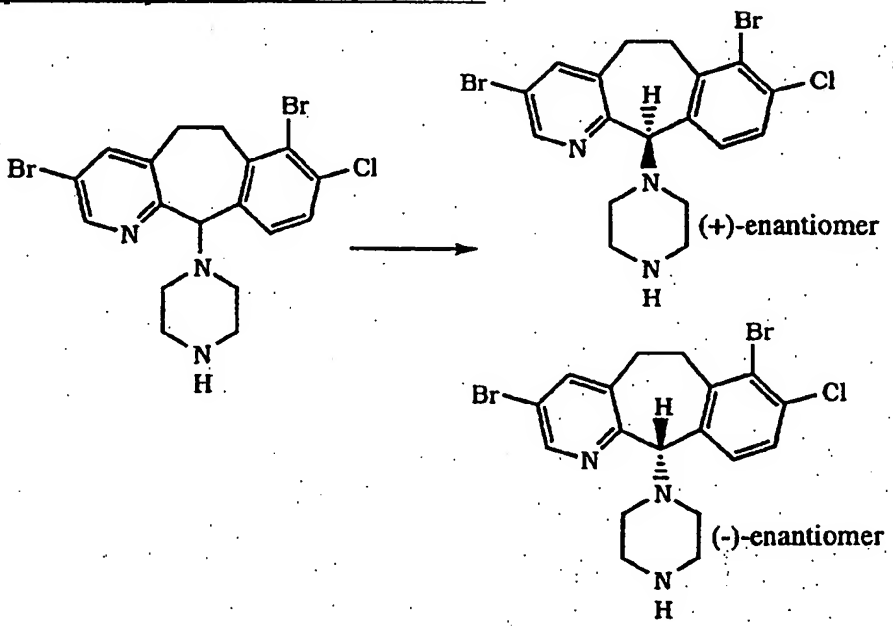
Combine 21.58 g (53.75 mmol) of the product of Step A and 500 mL of an anhydrous 1:1 mixture of EtOH and toluene, add 1.43 g (37.8 mmol) of $NaBH_4$ and heat the mixture at reflux for 10 min. Cool the mixture to 0°C, add 100 mL of water, then adjust to pH≈ 4-5 with 1 M HCl (aqueous) while keeping the temperature <10°C. Add 250 mL of EtOAc and separate the layers. Wash the organic layer with brine (3 X 50 mL) then dry over Na_2SO_4. Concentrate *in vacuo* to a residue (24.01 g) and chromatograph the residue (silica gel, 30 % hexane/CH_2Cl_2) to give the product. Impure fractions were purified by rechromatography. A total of 18.57 g of the product was obtained. ^1H NMR (DMSO-d_6, 400 MHz): 8.5 (s, 1H); 7.9 (s, 1H); 7.5 (d of d, 2H); 6.2 (s, 1H); 6.1 (s, 1H); 3.5 (m, 1H); 3.4 (m, 1H); 3.2 (m, 2H).

Step C:



Combine 18.57 g (46.02 mmol) of the product of Step B and 500 mL of $CHCl_3$, then add 6.70 mL (91.2 mmol) of $SOCl_2$, and stir the mixture at room temperature for 4 hrs. Add a solution of 35.6 g (0.413 mole) of piperazine in 800 mL of THF over a period of 5 min. and stir the mixture for 1 hr. at room temperature. Heat the mixture at reflux overnight, then cool to room temperature and dilute the mixture with 1 L of CH_2Cl_2. Wash with water (5 X 200 mL), and extract the aqueous wash with $CHCl_3$ (3 X 100 mL). Combine all of the organic solutions, wash with brine (3 X 200 mL) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, gradient of 5%, 7.5%, 10% $MeOH/CH_2Cl_2 + NH_4OH$) to give 18.49 g of the title compound as a racemic mixture.

Step D - Separation of Enantiomers:

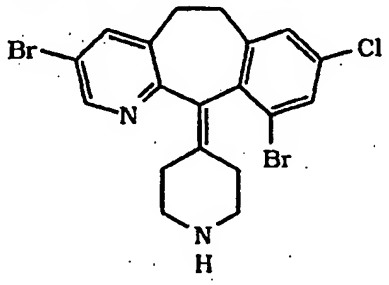


The racemic title compound of Step C is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 100 mL/min., 20% iPrOH/hexane + 0.2% diethylamine), to give 9.14 g of the (+)-enantiomer and 9.30 g of the (-)-enantiomer.

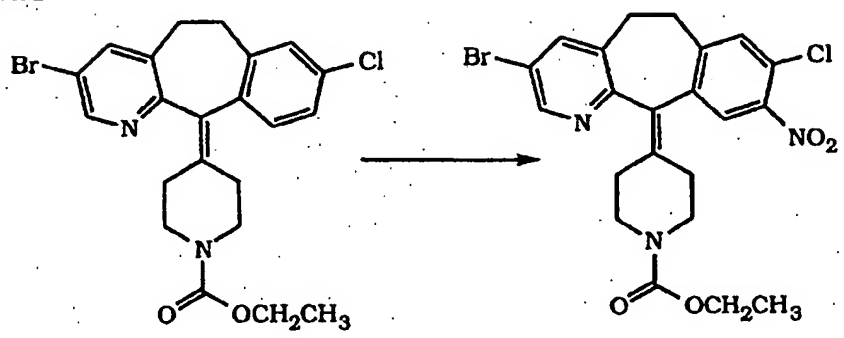
Physical chemical data for (+)-enantiomer: m.p. = 74.5°-77.5°C; Mass Spec. $MH^+ = 471.9$; $[\alpha]_D^{25}$ = +97.4° (8.48 mg/ 2mL MeOH).

Physical chemical data for (-)-enantiomer: m.p. = 82.9°-84.5°C; Mass Spec. $MH^+ = 471.8$; $[\alpha]_D^{25}$ = -97.4° (8.32 mg/ 2mL MeOH).

PREPARATIVE EXAMPLE 7



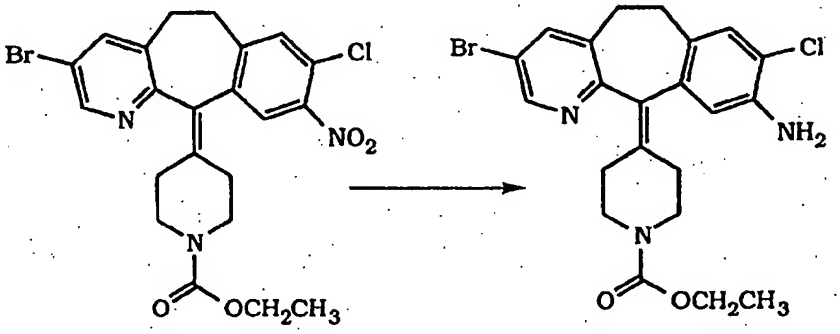
Step A:



Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of concentrated H_2SO_4 at -5°C, then add 3.89 g (38.5 mmol) of KNO_3 and stir for 4 hours. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product. ^1H NMR

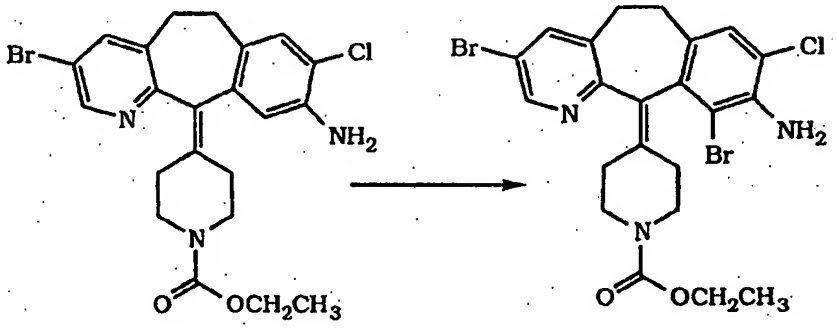
($CDCl_3$, 200 MHz): 8.5 (s, 1H); 7.75 (s, 1H); 7.6 (s, 1H); 7.35 (s, 1H); 4.15 (q, 2H); 3.8 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.8 (m, 2H); 2.6-2.2 (m, 4H); 1.25 (t, 3H). MH^+ = 506.

Step B:



Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, then add 0.66 g (5.9 mmol) of $CaCl_2$ and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux overnight. Filter the hot reaction mixture through Celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product. Mass Spec.: MH^+ = 476.0.

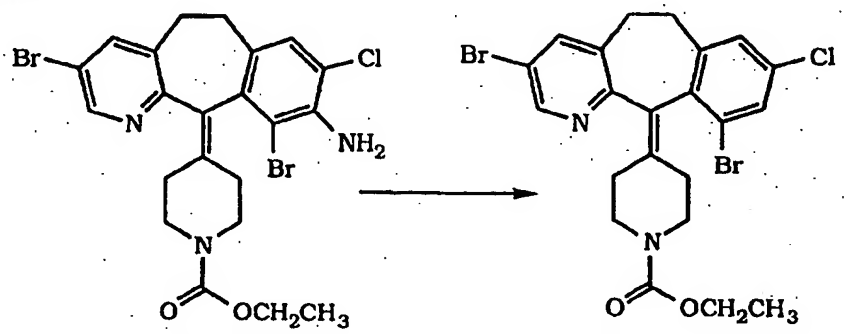
Step C:



Combine 7.70 g of the product of Step B and 35 mL of HOAc, then add 45 mL of a solution of Br_2 in HOAc and stir the mixture at room temperature overnight. Add 300 mL of 1 N NaOH (aqueous) , then 75 mL of 50% NaOH (aqueous) and extract with EtOAc. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 20%-30% EtOAc/hexane) to give 3.47 g of the product (along with another 1.28 g of partially purified product). Mass Spec.: MH^+ = 554.

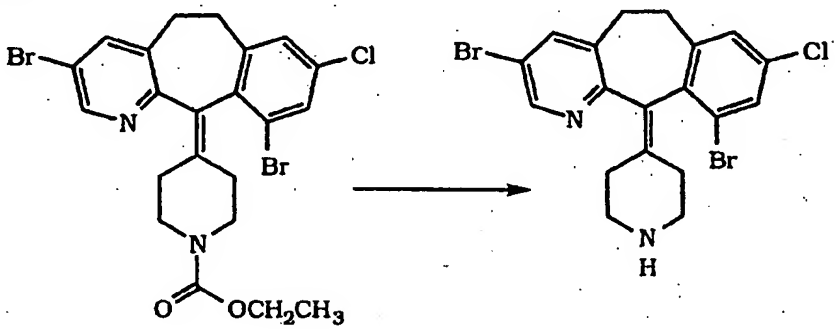
^{1}H NMR ($CDCl_3$, 300 MHz): 8.5 (s, 1H); 7.5 (s, 1H); 7.15 (s, 1H); 4.5 (s, 2H); 4.15 (m, 3H); 3.8 (br s, 2H); 3.4-3.1 (m, 4H); 9-2.75 (m, 1H); 2.7-2.5 (m, 2H); 2.4-2.2 (m, 2H); 1.25 (m, 3H).

Step D:



Combine 0.557 g (5.4 mmol) of t-butylnitrite and 3 mL of DMF, and heat the mixture at 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butylnitrite at 40°C and reheat the mixture to 60°-70°C for 0.5 hrs. Cool to room temperature and pour the mixture into 150 mL of water. Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10%-20% EtOAc/hexane) to give 0.74 g of the product. Mass Spec.: MH^+ = 539.0. ^{1}H NMR (CDCl3, 200 MHz): 8.52 (s, 1H); 7.5 (d, 2H); 7.2 (s, 1H); 4.15 (q, 2H); 3.9-3.7 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.5 (m, 2H); 2.4-2.2 (m, 2H); 2.1-1.9 (m, 2H); 1.26 (t, 3H).

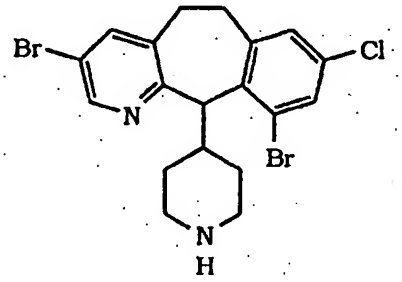
Step E:



Combine 0.70 g (1.4 mmol) of the product of Step D and 8 mL of concentrated HCl (aqueous) and heat the mixture at reflux

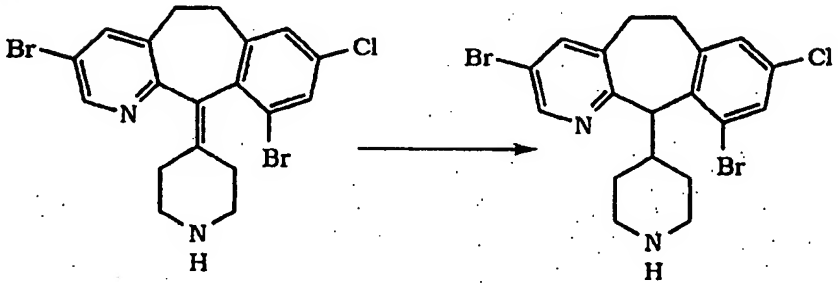
overnight. Add 30 mL of 1 N NaOH (aqueous), then 5 mL of 50% NaOH (aqueous) and extract with CH_2Cl_2. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 0.59 g of the title compound. Mass Spec.: MH^+ = 467. m.p. = 123.9°-124.2°C.

PREPARATIVE EXAMPLE 8



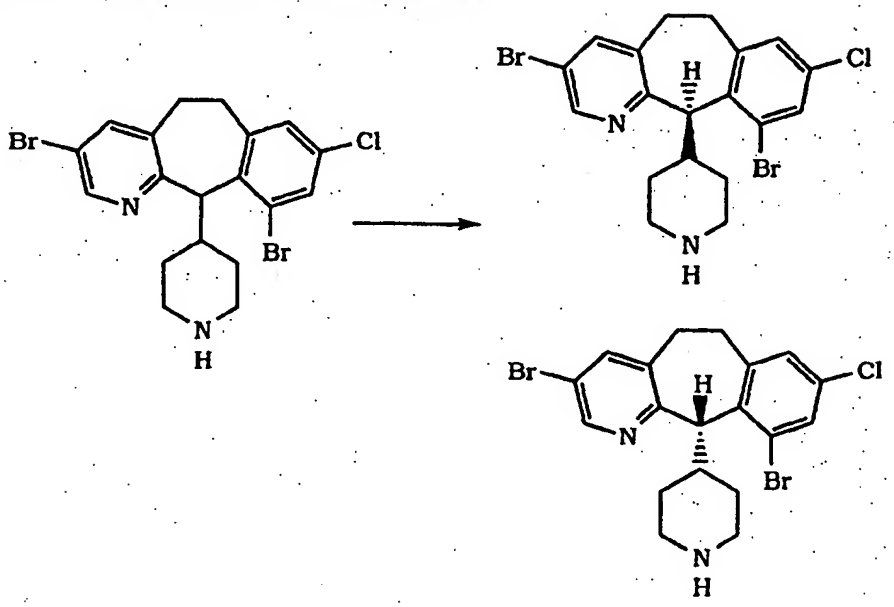
[racemic as well as (+)- and (-)-enantiomers]

Step A:



Prepare a solution of 8.1 g of the title compound from Preparative Example 7 in toluene and add 17.3 mL of a 1M solution of DIBAL in toluene. Heat the mixture at reflux and slowly add (dropwise) another 21 mL of 1 M DIBAL/toluene solution over a period of 40 min. Cool the reaction mixture to about 0°C and add 700 mL of 1 M HCl (aqueous). Separate and discard the organic phase. Wash the aqueous phase with CH_2Cl_2, discard the extract, then basify the aqueous phase by adding 50% NaOH (aqueous). Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 7.30 g of the title compound, which is a racemic mixture of enantiomers. MH^+ = 469.

Step B - Separation of Enantiomers:

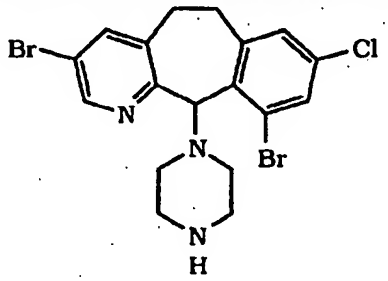


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20% iPrOH/hexane + 0.2% diethylamine), to give the (+)-enantiomer and the (-)-enantiomer of the title compound.

Physical chemical data for (+)-enantiomer: m.p. = 148.8°C; Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25} = +65.6°$ (12.93mg/2mL MeOH).

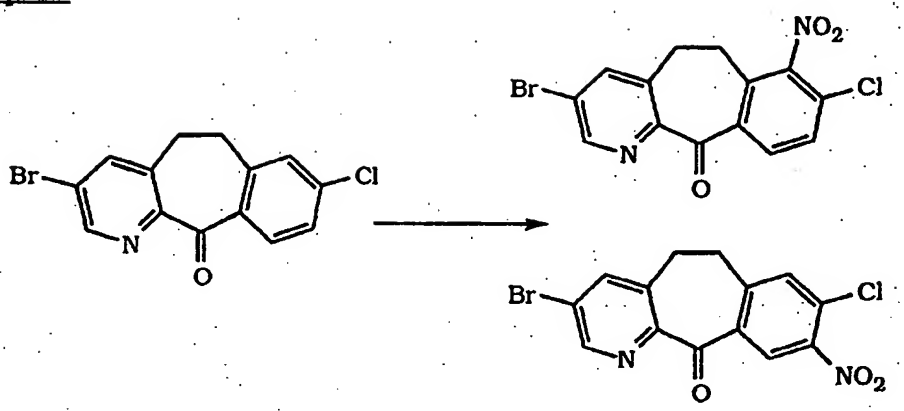
Physical chemical data for (-)-enantiomer: m.p. = 112°C; Mass Spec. $MH^+ = 469$; $[\alpha]_D^{25} = -65.2°$ (3.65mg/2mL MeOH).

PREPARATIVE EXAMPLE 9



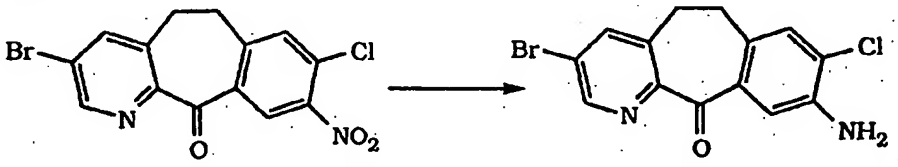
[racemic as well as (+)- and (-)-enantiomer]

Step A:



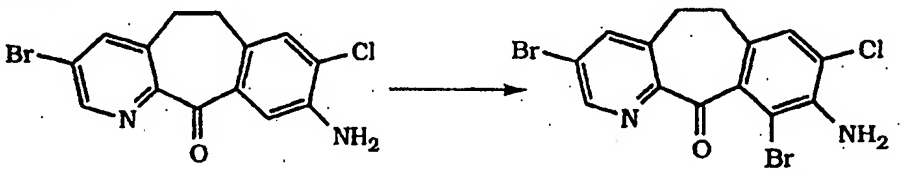
Combine 40.0 g (0.124 mole) of the starting ketone and 200 mL of H_2SO_4 and cool to 0°C. Slowly add 13.78 g (0.136 mole) of KNO_3 over a period of 1.5 hrs., then warm to room temperature and stir overnight. Work up the reaction using substantially the same procedure as described for Preparative Example 4, Step A. Chromatograph (silica gel, 20%, 30%, 40%, 50% EtOAc/hexane, then 100% EtOAc) to give 28 g of the 9-nitro product, along with a smaller quantity of the 7-nitro product and 19 g of a mixture of the 7-nitro and 9-nitro compounds. MH^+ (9-nitro) = 367.

Step B:



React 28 g (76.2 mmol) of the 9-nitro product of Step A, 400 mL of 85% EtOH/water, 3.8 g (34.3 mmol) of $CaCl_2$ and 38.28 g (0.685 mole) of Fe using substantially the same procedure as described for Preparative Example 4, Step C, to give 24 g of the product. MH^+ = 337.

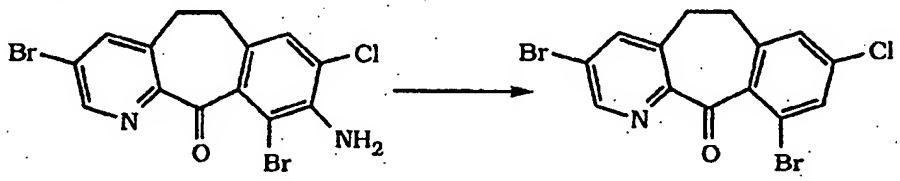
Step C:



Combine 13 g (38.5 mmol) of the product of Step B, 140 mL of HOAc and slowly add a solution of 2.95 mL (57.8 mmol) of Br_2 in 10 mL of HOAc over a period of 20 min. Stir the reaction mixture at room temperature, then concentrate *in vacuo* to a residue. Add CH_2Cl_2 and water, then adjust to pH = 8-9 with 50% NaOH (aqueous). Wash the organic phase with water, then brine and dry over Na_2SO_4. Concentrate *in vacuo* to give 11.3 g of the product.

^1H NMR (200 MHZ, $CDCl_3$): 8.73 (d, 1H); 7.74 (d, 1H); 7.14 (s, 1H); 4.63 (s, 2H); 3.23-3.15 (m, 2H); and 3.07-2.98 (m, 2H).

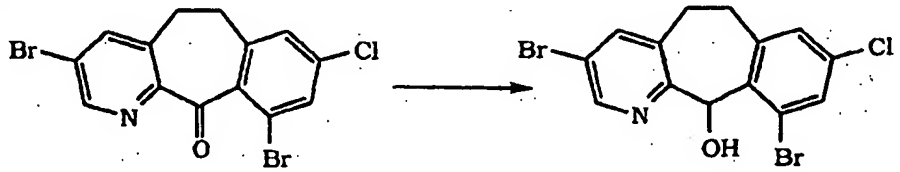
Step D:



Cool 100 mL of concentrated HCl (aqueous) to 0°C, then add 5.61 g (81.4 mmol) of $NaNO_2$ and stir for 10 min. Slowly add (in portions) 11.3 g (27.1 mmol) of the product of Step C and stir the mixture at 0°-3°C for 2.25 hrs. Slowly add (dropwise) 180 mL of 50% H_3PO_2 (aqueous) and allow the mixture to stand at 0°C overnight. Slowly add (dropwise) 150 mL of 50% NaOH over 30 min., to adjust to pH = 9, then extract with CH_2Cl_2. Wash the extract with water, then brine and dry over Na_2SO_4. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% EtOAc/ CH_2Cl_2) to give 8.6 g of the product. MH^+ = 399.9.

^1H NMR (200 MHZ, $CDCl_3$): 8.75 (d, 1H); 7.77 (d, 1H); 7.56 (d, 1H); 7.21 (d, 1H); and 3.3-3.0 (m, 4H).

Step E:

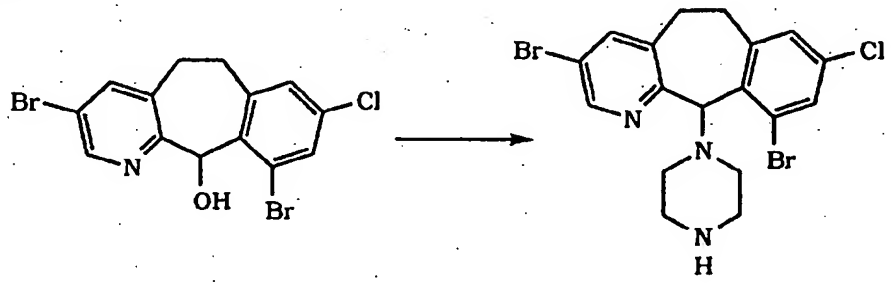


Combine 8.6 g (21.4 mmol) of the product of Step D and 300 mL of MeOH and cool to 0°-2°C. Add 1.21 g (32.1 mmol) of

$NaBH_4$ and stir the mixture at ~0°C for 1 hr. Add another 0.121 g (3.21 mmol) of $NaBH_4$, stir for 2 hr. at 0°C, then let stand overnight at 0°C. Concentrate *in vacuo* to a residue then partition the residue between CH_2Cl_2 and water. Separate the organic phase and concentrate *in vacuo* (50°C) to give 8.2 g of the product.

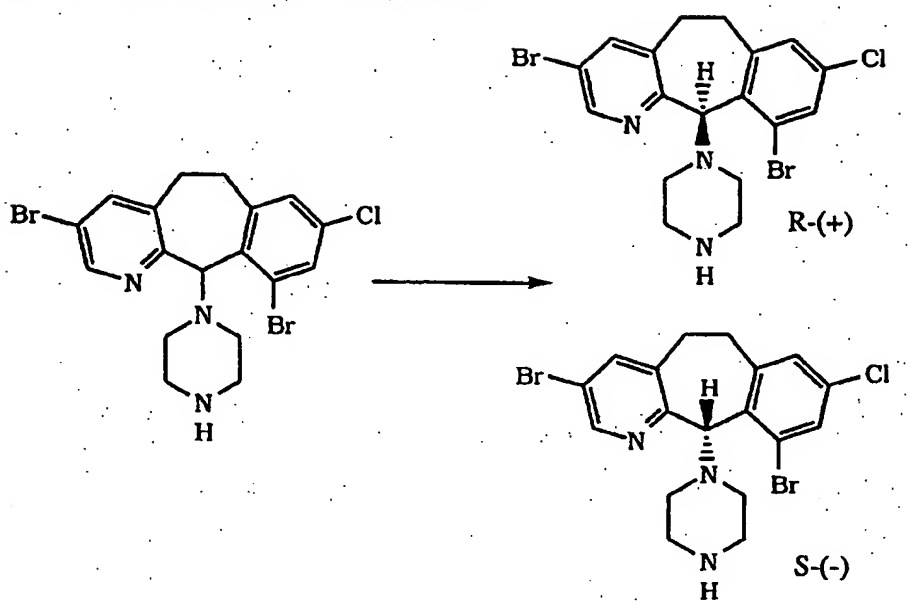
^1H NMR (200 MHZ, $CDCl_3$): 8.44 (d, 1H); 7.63 (d, 1H); 7.47 (d, 1H); 7.17 (d, 1H); 6.56 (d, 1H); 4.17-4.0 (m, 1H); 7.39 (d, 1H); 3.46-3.3 (m, 1H); 3.05-2.74 (m, 2H).

Step F:



Combine 8.2 g (20.3 mmol) of the product of Step E and 160 mL of CH_2Cl_2, cool to 0°C, then slowly add (dropwise) 14.8 mL (203 mmol) of $SOCl_2$ over a 30 min. period. Warm the mixture to room temperature and stir for 4.5 hrs., then concentrate *in vacuo* to a residue, add CH_2Cl_2 and wash with 1 N NaOH (aqueous) then brine and dry over Na_2SO_4. Concentrate *in vacuo* to a residue, then add dry THF and 8.7 g (101 mmol) of piperazine and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add CH_2Cl_2, and wash with 0.25 N NaOH (aqueous), water, then brine. Dry over Na_2SO_4 and concentrate *in vacuo* to give 9.46 g of the crude product. Chromatograph (silica gel, 5% MeOH/CH_2Cl_2 + NH_3) to give 3.59 g of the title compound, as a racemate. ^1H NMR ($CDCl_3$, 200 MHz): 8.43 (d, 1H); 7.55 (d, 1H); 7.45 (d, 1H); 7.11 (d, 1H); 5.31 (s, 1H); 4.86-4.65 (m, 1H); 3.57-3.40 (m, 1H); 2.98-2.55 (m, 6H); 2.45-2.20 (m, 5H). MH^+ = 470.

Step G - Separation of Enantiomers:

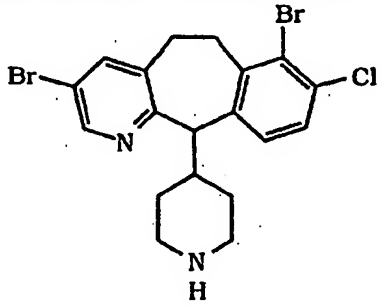


The racemic title compound from Step F (5.7 g) is chromatographed as described for Preparative Example 6, Step D, using 30% iPrOH/hexane + 0.2% diethylamine, to give 2.88 g of the R-(+)-enantiomer and 2.77 g of the S-(-)-enantiomer of the title compound.

Physical chemical data for the R-(+)-enantiomer: Mass Spec. $MH^+ = 470$; $[\alpha]_D^{25} = +12.1°$ (10.9 mg/ 2mL MeOH).

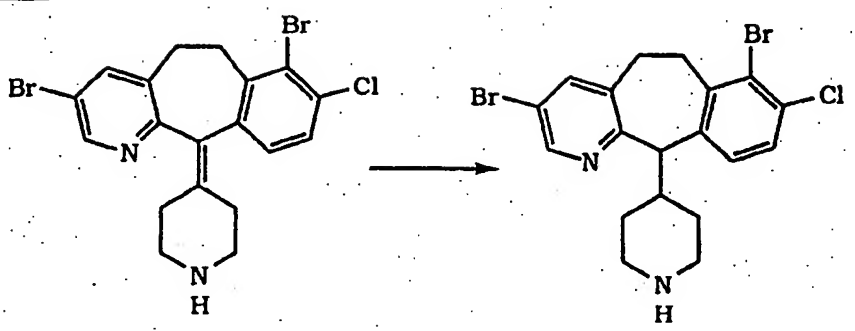
Physical chemical data for the S-(-)-enantiomer: Mass Spec. $MH^+ = 470$; $[\alpha]_D^{25} = -13.2°$ (11.51 mg/ 2mL MeOH).

PREPARATIVE EXAMPLE 10



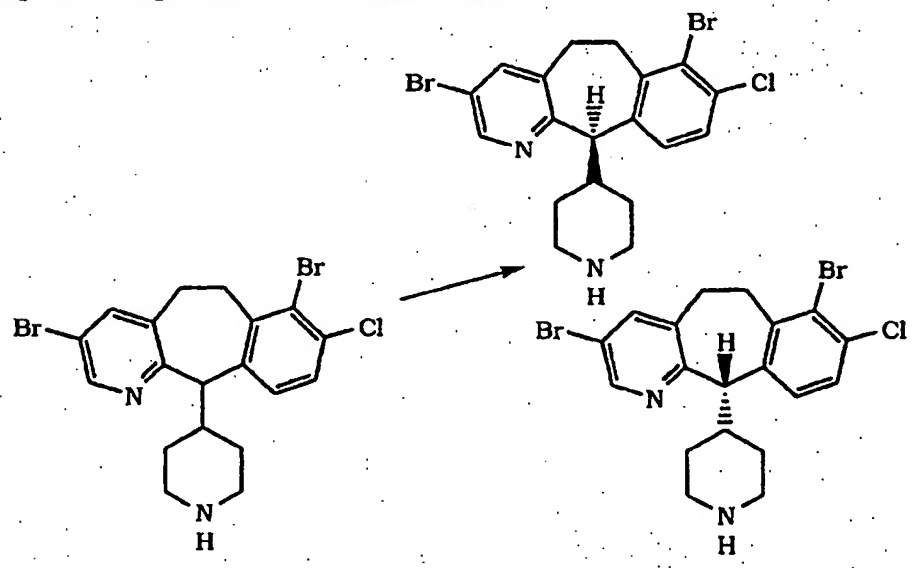
[racemic as well as (+)- and (-)-enantiomer]

Step A:



Combine 13 g (33.3 mmol) of the title compound from Preparative Example 4, Step D, and 300 mL of toluene at 20°C, then add 32.5 mL (32.5 mmol) of a 1 M solution of DIBAL in toluene. Heat the mixture at reflux for 1 hr., cool to 20°C, add another 32.5 mL of 1 M DIBAL solution and heat at reflux for 1 hr. Cool the mixture to 20°C and pour it into a mixture of 400 g of ice, 500 mL of EtOAc and 300 mL of 10% NaOH (aqueous). Extract the aqueous layer with CH_2Cl_2 (3 x 200 mL), dry the organic layers over $MgSO_4$, then concentrate *in vacuo* to a residue. Chromatograph (silica gel, 12% MeOH/CH_2Cl_2 + 4% NH_4OH) to give 10.4 g of the title compound as a racemate. Mass Spec.: MH^+ = 469 (FAB). partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.06 (d, 1H); 3.95 (d, 1H).

Step B - Separation of Enantiomers:

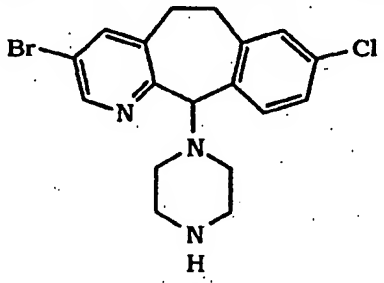


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 5% iPrOH/hexane + 0.2% diethylamine), to give the (+)-enantiomer and the (-)-enantiomer of the title compound.

Physical chemical data for (+)-enantiomer: Mass Spec. $MH^+ = 469$ (FABS); $[\alpha]_D^{25} = +43.5°$ (c=0.402, EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

Physical chemical data for (-)-enantiomer: Mass Spec. $MH^+ = 469$ (FAB); $[\alpha]_D^{25} = -41.8°$ (c=0.328 EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

PREPARATIVE EXAMPLE 11



[racemic as well as R-(+)- and S-(-)-enantiomer]

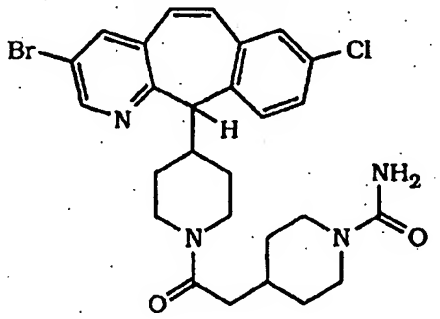
Treat 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester via substantially the same procedure as described in Preparative Example 6, Steps A-D, to give as the product of Step C, the racemic title compound, and as the products of Step D the R-(+)-enantiomer and S-(-)-enantiomer of the title compound.

Physical chemical data for the R-(+)-enantiomer: ^{13}C NMR ($CDCl_3$): 155.8 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C); 135.3 (C); 133.4 (C); 132.0 (CH); 129.9 (CH); 125.6 (CH); 119.3 (C); 79.1 (CH); 52.3 (CH_2); 52.3 (CH_2); 45.6 (CH_2); 45.6 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[\alpha]_D^{25} = +25.8°$ (8.46 mg/2 mL MeOH).

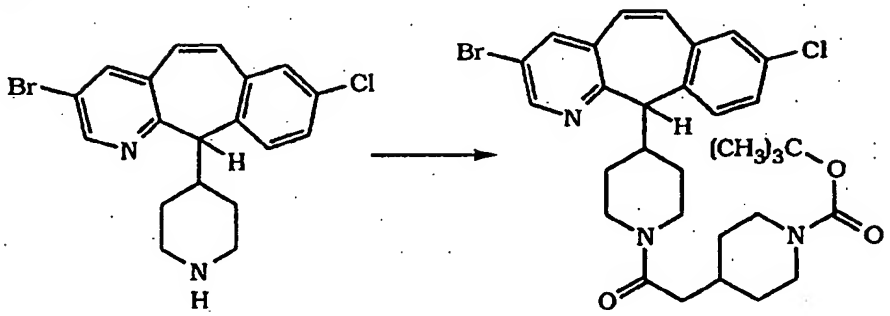
Physical chemical data for the S-(-)-enantiomer: ^{13}C NMR ($CDCl_3$): 155.9 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C);

135.3 (C); 133.3 (C); 132.0 (CH); 129.9 (CH); 125.5 (CH); 119.2 (C); 79.1 (CH); 52.5 (CH_2); 52.5 (CH_2); 45.7 (CH_2); 45.7 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[\alpha]_D^{25}$ = -27.9° (8.90 mg/2 mL MeOH).

EXAMPLE 1



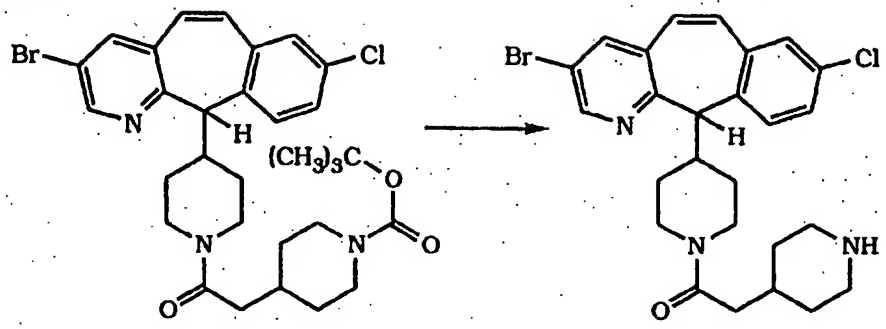
Step A:



Dissolve 1.160 g (2.98 mmol) of the title compound from Preparative Example 3 in 20 mL of DMF, stir at room temperature, and add 0.3914 g (3.87 mmol) of 4-methyl-morpholine, 0.7418 g (3.87 mmol) of DEC, 0.5229 g (3.87 mmol) of HOBT, and 0.8795 g (3.87 mmol) of 1-N-t-butoxycarbonyl-piperidinyl-4-acetic acid. Stir the mixture at room temperature for 2 days, then concentrate *in vacuo* to a residue and partition the residue between CH_2Cl_2 and water. Wash the organic phase successively with saturated $NaHCO_3$ (aqueous), 10% NaH_2PO_4 (aqueous) and brine. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 2% MeOH/ CH_2Cl_2 + NH_3) to give 1.72 g of the product. m.p. = 94.0-94.5°C, Mass Spec.: MH^+ = 614.

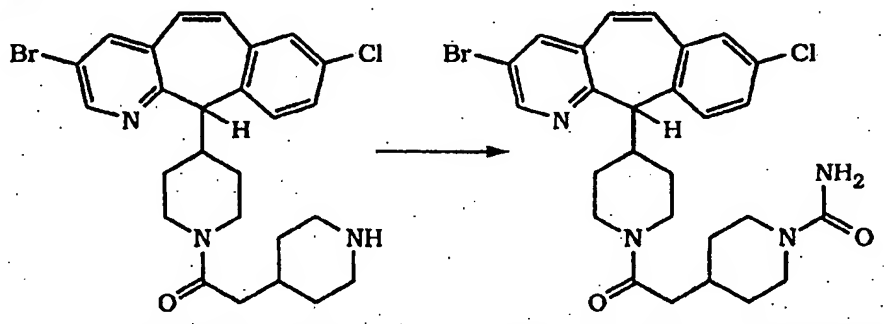
Elemental analysis: calculated - C, 60.54; H, 6.06; N, 6.83
found - C, 59.93; H, 6.62; N, 7.45.

Step B:



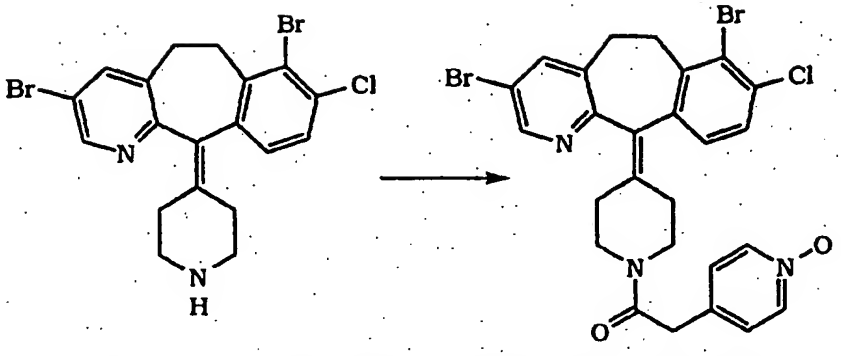
Combine 1.67 g (2.7 mmol) of the product of Step A and 20 mL of CH_2Cl_2 and stir at 0°C. Add 20 mL of TFA, stir the mixture for 2 hours, then basify the mixture with 1 N NaOH (aqueous). Extract with CH_2Cl_2, dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo* to give 1.16 g of the product. m.p. = 140.2-140.8°C, Mass Spec.: MH^+ = 514.

Step C:



Combine 0.50 g of the product of Step B, 20 mL of CH_2Cl_2 and 4.5 equivalents of $(CH_3)_3SiNCO$ and stir at room temperature for 3 hours. Extract the mixture with saturated $NaHCO_3$ (aqueous) and dry the organic phase over $MgSO_4$. Filter and concentrate *in vacuo* to give 0.8 g of the crude product. Chromatograph the crude product (silica gel, 5% MeOH/CH_2Cl_2 + NH_3) to give 0.26 g of the product. m.p. = 170.2-170.5°C, Mass Spec.: MH^+ = 557.

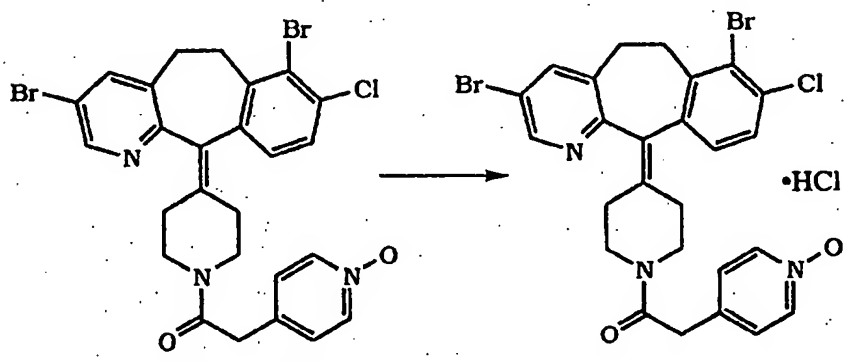
EXAMPLE 2



Combine 0.5 g (1.06 mmol) of the title compound of Preparative Example 4, 0.4 g (2.61 mmol) of the title compound of Preparative Example 1, 5 mL of dry DMF, and 0.5 mL (4.53 mmol) of 4-methylmorpholine, at 0°C, then add 0.6 g (3.12 mmol) of DEC and 0.4 g (2.96 mmol) of HOBT and stir the mixture overnight at 20°C. Concentrate *in vacuo* to a residue and extract the residue with CH_2Cl_2 (2 X 50 mL). Wash the extracts with 25 mL of water, dry over $MgSO_4$, then concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aqueous)) to give 0.6 g (93.7% yield) of the title compound. Mass Spec.: MH^+ = 602 (FABS); partial ^1H NMR ($CDCl_3$, 300 MHz): 8.48 (s, 1H); 8.16 (d, 2H); 7.61 (s, 1H); 7.29 (m, 1H); 7.18 (d, 2H); 7.04 (d, 1H); 3.71 (s, 2H).

Elemental analysis: calculated - C, 48.81; H, 4.10; N, 6.57
found - C, 49.10; H, 3.79; N, 6.74.

EXAMPLE 3



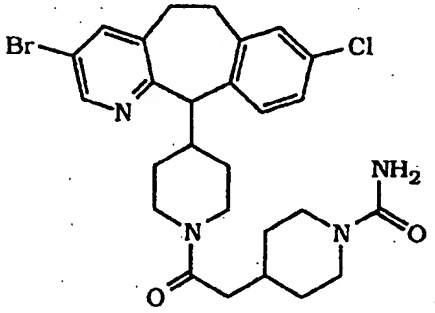
Dissolve 5.9 g (9.78 mmol) of the title compound of Example 2 in 300 mL of 1:5 CH_2Cl_2/EtOAc at 0°C. Slowly add

(dropwise) 3 mL of 4 N HCl (aqueous) and stir the mixture at 0°C for 5 min. Add 200 mL of Et_2O, collect the resulting solids by filtration and wash the solids with 50 mL of Et_2O. Dry the solids at 20°C and 0.2 mm Hg to give 5.9 g (96% yield) of the title compound. Mass Spec.: MH^+ = 602 (FAB).

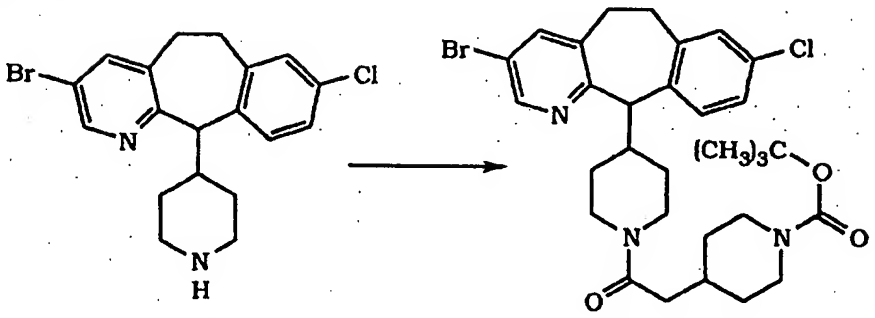
partial ^1H NMR (DMSO-d_6, 300 MHz): δ 8.66 (d, 2H); 8.51 (s, 1H); 7.95 (s, 1H); 7.67 (d, 2H); 7.47 (m, 1H); 7.15 (m, 1H); 3.99 (s, 2H).

Elemental analysis: calculated - C, 48.77; H, 3.62; N, 6.56
found - C, 48.34; H, 3.95; N, 6.84.

EXAMPLE 4



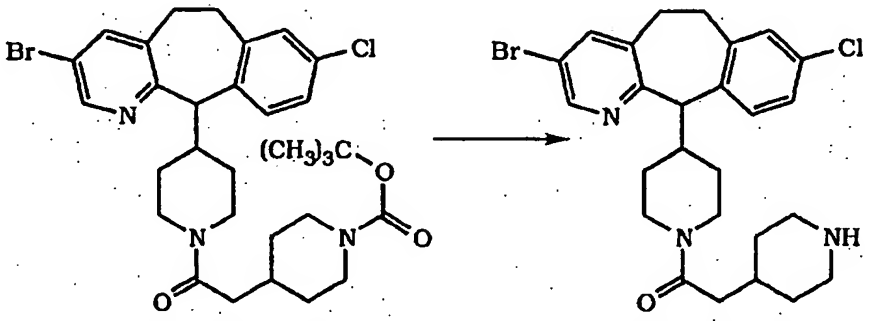
Step A:



Combine 0.501 g (1.28 mmol) of the title compound of Preparative Example 5 and 20 mL of dry DMF, then add 0.405 g (1.664 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid, 0.319 g (1.664 mmol) of DEC, 0.225 g (1.664 mmol) of HOBT, and 0.168 g (1.664 mmol) of 4-methylmorpholine and stir the mixture at room temperature overnight. Concentrate the mixture *in vacuo* to a residue, then partition the residue between 150 mL of CH_2Cl_2 and 150 mL of saturated $NaHCO_3$ (aqueous). Extract the aqueous phase with another 150 mL of

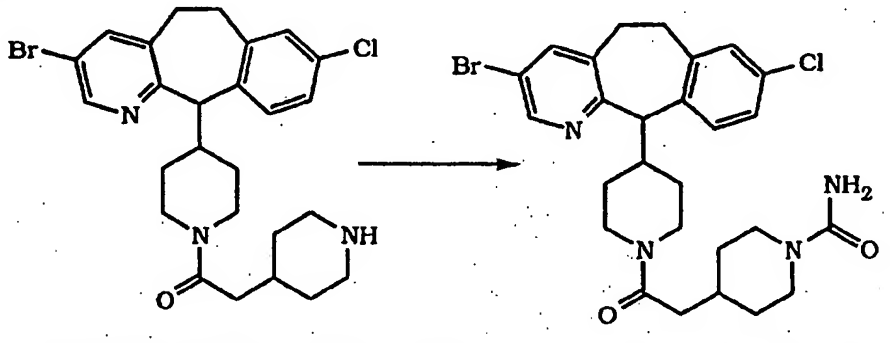
CH_2Cl_2. Dry the organic phase over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL hexane, 1 L of 1% MeOH/CH_2Cl_2 + 0.1% NH_4OH (aqueous), then 1 L of 2% MeOH/CH_2Cl_2 + 0.1% NH_4OH (aqueous)) to give 0.575 g of the product. m.p. = 115°-125°C; Mass Spec.: MH^+ = 616.

Step B:



Combine 0.555 g (0.9 mmol) of the product of Step A and 15 mL of CH_2Cl_2 and cool the mixture to 0°C. Add 15 mL of TFA and stir at 0°C for 2 hours. Concentrate *in vacuo* at 40-45°C to a residue, then partition the residue between 150 mL of CH_2Cl_2 and 100 mL of saturated $NaHCO_3$ (aqueous). Extract the aqueous layer with 100 mL of CH_2Cl_2, combine the extracts and dry over $MgSO_4$. Concentrate *in vacuo* to give 0.47 g of the product. m.p. = 140°-150°C; Mass Spec.: MH^+ = 516.

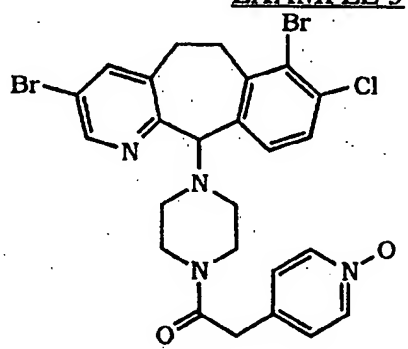
Step C:



Combine 0.449 g (0.87 mmol) of the product of Step B, 20 mL of CH_2Cl_2 and 0.501 g (0.59 mmol) of $(CH_3)_3SiNCO$ and stir at room temperature overnight. Add 50-75 mL of saturated $NaHCO_3$ (aqueous) and stir for 0.5 hours. Dilute with CH_2Cl_2,

separate the layers and extract the aqueous layer with 2 X 100 mL of CH_2Cl_2. Dry the combined CH_2Cl_2 extracts over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL CH_2Cl_2; 1 L of 1% MeOH/CH_2Cl_2 + 0.1% NH_4OH; 1 L of 2% MeOH/CH_2Cl_2 + 0.2% NH_4OH; then with 3% MeOH/CH_2Cl_2 + 0.3% NH_4OH) to give 0.33 g of the title compound. m.p. = 145°-155°C; Mass Spec.: MH^+ = 559.

EXAMPLE 5



(-)-enantiomer

Combine 3.0 g (6.36 mmol) of the (-)-enantiomer of the title compound from Preparative Example 6, Step D, and 70 mL of dry DMF. Add 3.84 mL (34.94 mmol) of N-methylmorpholine, 3.28 g (17.11 mmol) of DEC, 2.23 g (16.52 mmol) of HOBT and 2.09 (13.55 mmol) of 4-pyridylacetic acid N-oxide from Preparative Example 1 and stir the mixture at room temperature overnight. Concentrate *in vacuo* to remove the DMF, add 100 mL of saturated $NaHCO_3$ (aqueous) and 10 mL of CH_2Cl_2 and stir for 15 min. Extract the mixture with CH_2Cl_2 (2 X 500 mL), dry the extracts over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (500 g reverse phase C18 silica, gradient of 75%, 80%, then 85% MeOH/water + 0.1% HOAc). Concentrate the desired fractions *in vacuo* to remove MeOH and add 50 mL of 1 M NaOH (aqueous). Stir for 15 min., then extract with CH_2Cl_2 (2 X 500 mL). Dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 3.4 g of the title compound. m.p. = 148.9°-150.5°C; $[\alpha]_D^{25}$ = -56.37° (9.4 mg/2mL MeOH); Mass Spec. MH^+ = 605.

The title compound of Example 5 can also be isolated as its HCl salt by treating a solution of the product in HCl and CH_2Cl_2 at

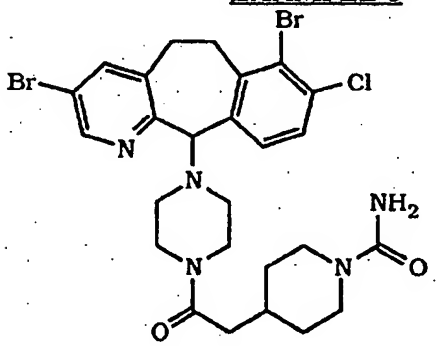
room temperature, followed by concentration *in vacuo* to give the HCl salt. $[\alpha]_D^{25}$ = -31.9° (4.80 mg/2 mL MeOH + 1 mL of water).

Using the (+)-enantiomer of the product of Preparative Example 6 and following essentially the same procedure as described above for Example 5, the analogous (+)-enantiomer (Example 5A), i.e., the enantiomer of the title compound of Example 5, is prepared. m.p. = 149.0°-150.5°C; Mass Spec.: MH^+ = 605; $[\alpha]_D^{25}$ = +67.1° (7.0 mg/2mL MeOH).

The title compound of Example 5A can also be isolated as its HCl salt as described above for Example 5. m.p. = 152.9°C (dec.); $[\alpha]_D^{25}$ = +41.7° (2 mL MeOH + 1 mL of water).

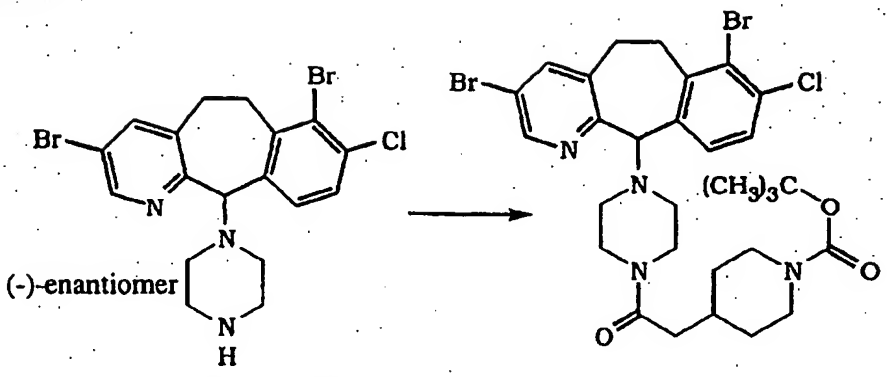
Using the racemic title compound of Preparative Example 6, Step C, and following essentially the same procedure as described above for Example 5, the racemate (Example 5B), is prepared. m.p. = 84.3°-85.6°C; Mass Spec.: MH^+ = 607.

EXAMPLE 6



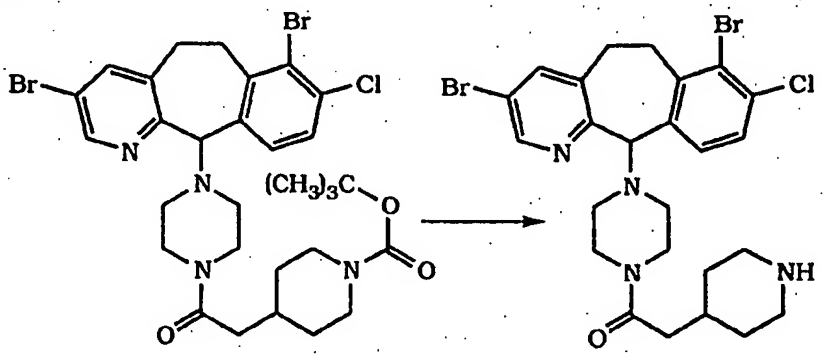
(-)-enantiomer

Step A:



Combine 3.21 g (6.80 mmol) of the (-)-enantiomer product of Preparative Example 6 and 150 mL of anhydrous DMF. Add 2.15 g (8.8 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid, 1.69 g (8.8 mmol) of DEC, 1.19 g (8.8 mmol) of HOBT and 0.97 mL (8.8 mmol) of N-methylmorpholine and stir the mixture at room temperature overnight. Concentrate *in vacuo* to remove the DMF and add 50 mL of saturated $NaHCO_3$ (aqueous). Extract with CH_2Cl_2 (2 X 250 mL), wash the extracts with 50 mL of brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% MeOH/CH_2Cl_2 + 10% NH_4OH) to give 4.75 g of the product. m.p. = 75.7°-78.5°C; Mass Spec.: MH^+ = 695; $[\alpha]_D^{25}$ = -5.5° (6.6 mg/2 mL MeOH).

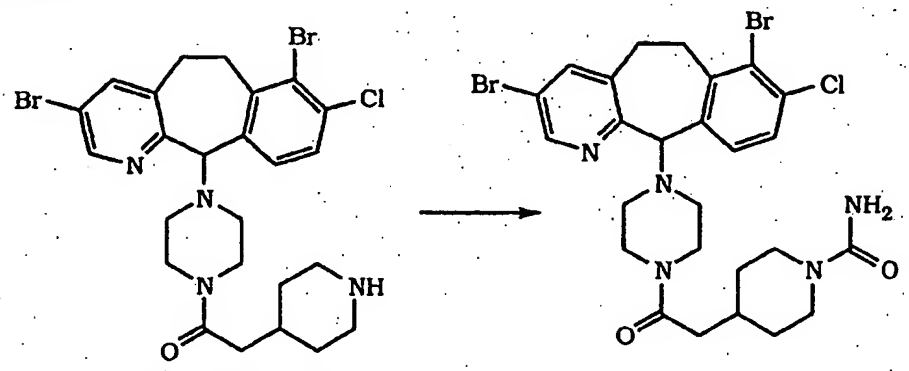
Step B:



Combine 4.70 g (6.74 mmol) of the product of Step A and 30 mL of MeOH, then add 50 mL of 10% H_2SO_4/dioxane in 10 mL aliquots over a 1 hr. period. Pour the mixture into 50 mL of water and add 15 mL of 50% NaOH (aqueous) to adjust to pH= 10-11. Filter to remove the resulting solids and extract the filtrate with CH_2Cl_2 (2 X 250 mL). Concentrate the aqueous

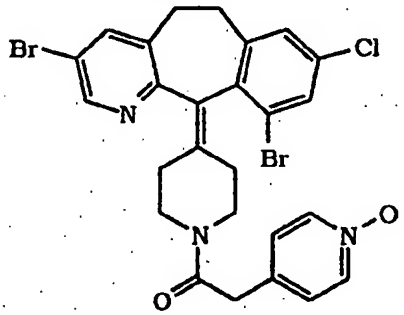
layer *in vacuo* to remove the MeOH and extract again with 250 mL of CH_2Cl_2. Dry the combined extracts over $MgSO_4$ and concentrate *in vacuo* to give the product. m.p. = 128.1°-131.5°C; Mass Spec.: $MH^+ = 595$; $[\alpha]_D^{25} = -6.02°$ (9.3 mg/2 mL MeOH).

Step C:



Combine 3.64 g (5.58 mmol) of the product of Step B and 30 mL of CH_2Cl_2, then add 6.29 mL (44.64 mmol) of $(CH_3)_3SiNCO$ and stir the mixture for 2 days at room temperature. Add 25 mL of $NaHCO_3$ (aqueous), then extract with CH_2Cl_2 (2 X 250 mL). Wash the extracts with 25 mL of brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, gradient of 2.5%, 5.0%, then 7.5% MeOH/CH_2Cl_2 + 10% NH_4OH) to give the title compound. m.p. = 150.5°-153.0°C; Mass Spec.: $MH^+ = 638$; $[\alpha]_D^{25} = -61.4°$ (8.18 mg/2 mL MeOH).

EXAMPLE 7

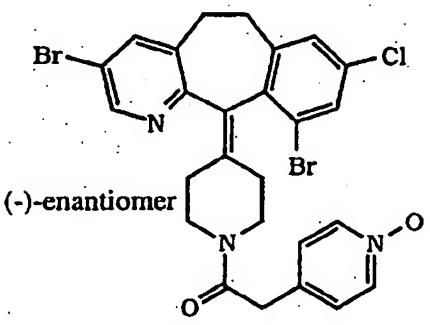


React the title compound of Preparative Example 7 and the title compound of Preparative Example 1 using substantially the same procedure as described for Example 2, to give 0.25 g of the

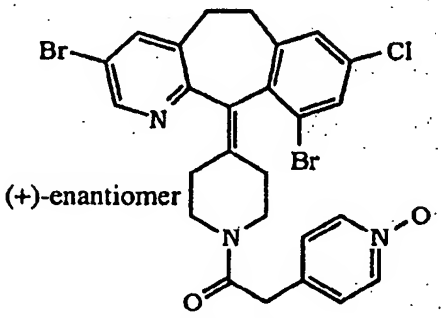
title compound, which is a racemic mixture of atropisomers. Mass Spec.: MH^+ = 602. m.p. = 167.2°-167.8°C.

The HCl salt of the title compound of Example 7 is prepared by stirring for 1 hr. with HCl/CH_2Cl_2, then concentrating *in vacuo* to give the salt.

EXAMPLES 7A & 7B



Example 7A



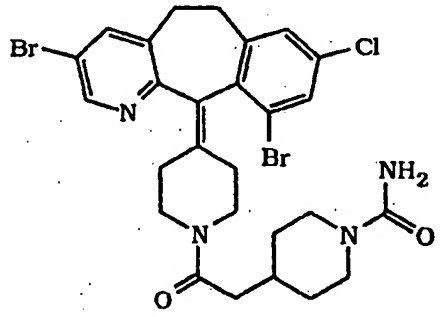
Example 7B

The title compound of Example 7 is a racemic mixture of atropisomers. Those atropisomers are separated by preparative chromatography (HPLC), using an Chiralpack AD column (5 cm x 50 cm) and 40% i-PrOH/ hexane + 0.2% diethylamine as the mobile phase to give the (+)- and (-)-enantiomers, Examples 7B and 7A, respectively.

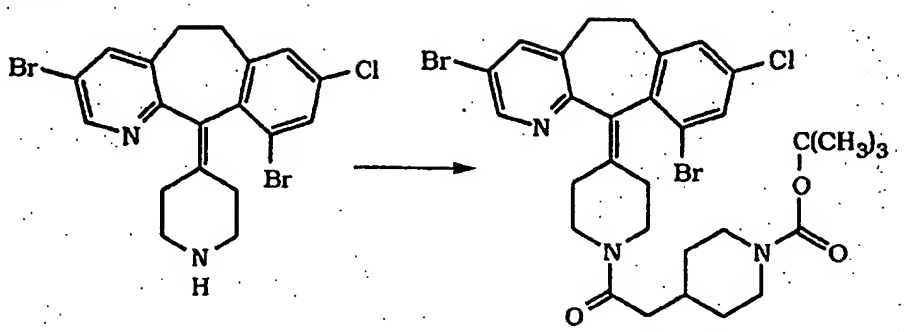
Physical chemical data for (-)-enantiomer, Example 7A: m.p. = 114.2°-114.8°C; $[\alpha]_D^{25}$ = -154.6° (8.73 mg/2 mL, MeOH).

Physical chemical data for (+)-enantiomer, Example 7B: m.p. = 112.6°-113.5°C; $[\alpha]_D^{25}$ = +159.7° (10.33 mg/2 mL, MeOH).

EXAMPLE 8

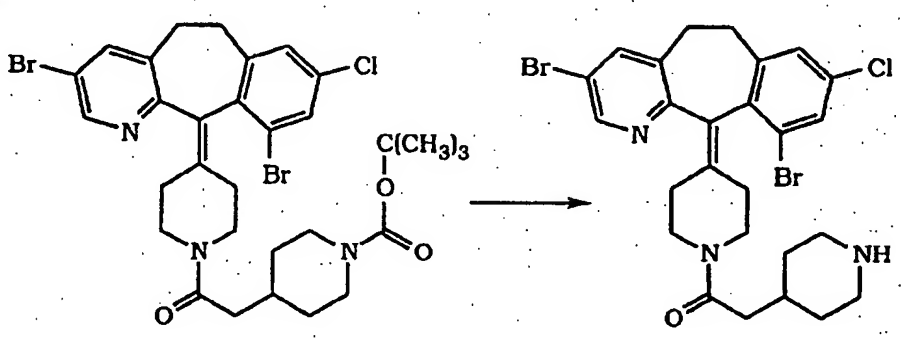


Step A:



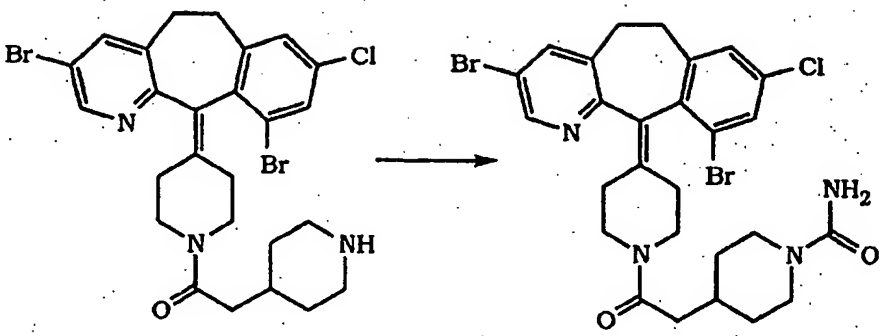
React 6.0 g (12.8 mmol) of the title compound of Preparative Example 7 and with 3.78 g (16.6 mmol) of 1-N-t-butoxycarbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Example 6, Step A, to give 8.52 g of the product. Mass Spec.: MH^+ = 692 (FAB). ^1H NMR ($CDCl_3$, 200 MHz): 8.5 (d, 1H); 7.5 (d, 2H); 7.2 (d, 1H); 4.15-3.9 (m, 3H); 3.8-3.6 (m, 1H); 3.5-3.15 (m, 3H); 2.9 (d, 2H); 2.8-2.5 (m, 4H); 2.4-1.8 (m, 6H); 1.8-1.6 (br d, 2H); 1.4 (s, 9H); 1.25-1.0 (m, 2H).

Step B:



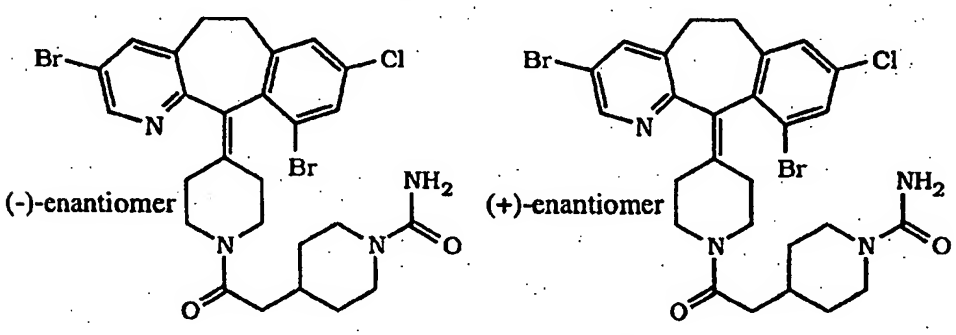
Combine 8.50 g of the product of Step A and 60 mL of CH_2Cl_2, then cool to 0°C and add 55 mL of TFA. Stir the mixture for 3 h at 0°C, then add 500 mL of 1 N NaOH (aqueous) followed by 30 mL of 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to give 7.86 g of the product. Mass Spec.: MH^+ = 592 (FAB). ^1H NMR ($CDCl_3$, 200 MHz): 8.51 (d, 1H); 7.52 (d of d, 2H); 7.20 (d, 1H); 4.1-3.95 (m, 2H); 3.8-3.65 (m, 2H); 3.5-3.05 (m, 5H); 3.0-2.5 (m, 6H); 2.45-1.6 (m, 6H); 1.4-1.1 (m, 2H).

Step C:



Treat 7.80 g (13.1 mmol) of the product of Step B with 12.1 g (105 mmol) of $(CH_3)_3SiNCO$ using substantially the same procedure as described for Example 6, Step C, to give 5.50 g of the title compound, which is a racemic mixture of atropisomers. m.p. = 163.6°-164.0°C. Mass spec.: MH^+ = 635 (FAB). ^1H NMR ($CDCl_3$, 200 MHz): 8.5 (d, 1H); 7.52 (d, 1H); 7.48 (d, 1H); 7.21 (d, 1H); 4.54, (s, 2H); 4.1-3.6 (m, 4H); 3.45-3.15 (m, 4H); 3.0-2.5 (m, 5H); 2.45-1.6 (m, 7H); 1.4-1.0, (m, 2H).

EXAMPLES 8A & 8B



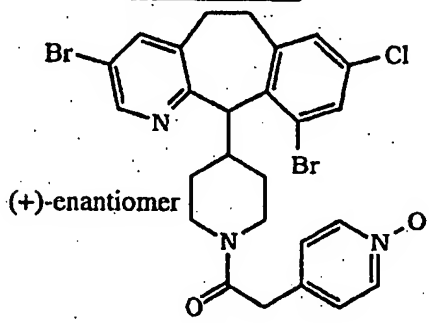
Example 8A Example 8B

The title compound of Example 8 is a racemic mixture of atropisomers. Those atropisomers are separated by preparative chromatography (HPLC), using an Chiralpack AD column (5 cm x 50 cm) and 20% i-PrOH/ hexane + 0.2% diethylamine as the mobile phase, at a flow rate of 100 mL/min., to give the (+)- and (-)-enantiomers, Examples 8B and 8A, respectively.

Physical chemical data for (-)-enantiomer, Example 8A: m.p. = 142.9°-143.5°C; $[\alpha]_D^{25}$ = -151.7° (11.06 mg/2 mL, MeOH).

Physical chemical data for (+)-enantiomer, Example 8B: m.p. = 126.5°-127.0°C; $[\alpha]_D^{25}$ = +145.6° (8.38 mg/2 mL, MeOH).

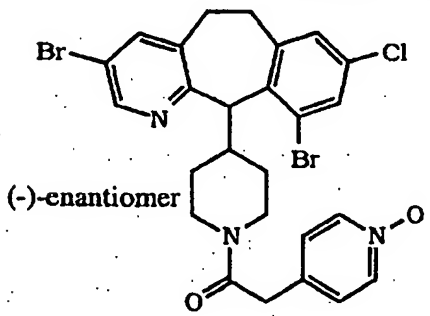
EXAMPLE 9



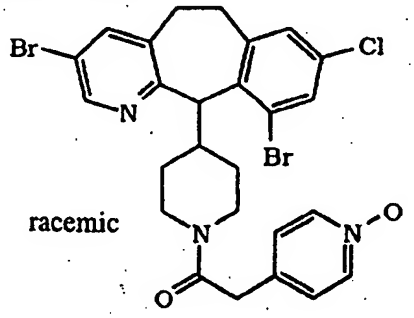
Combine 3.32 g of the (+)-enantiomer of the title compound of Preparative Example 8, Step B, 2.38 g of the title compound of Preparative Example 1, 1.92 g of HOBT, 2.70 g of DEC, 1.56 mL of N-methylmorpholine and 50 mL of dry DMF and stir at 25°C for 24 hrs. Concentrate *in vacuo*, then dilute the residue with CH_2Cl_2. Wash with 1 N NaOH (aqueous), then with saturated NaH_2PO_4 (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% $MeOH/CH_2Cl_2$ + NH_4OH) to give 3.82 g of the title compound. Mass Spec.: MH^+ = 604 (FAB).

The hydrochloride salt was prepared by dissolution of the title compound from Example 9 in dichloromethane saturated with hydrogen chloride. Concentration *in vacuo* provided the title compound from Example 9 as the HCl salt. m.p. = 166.5°C; $[\alpha]_D^{22}$ = +70.8° (9.9mg/2mL MeOH).

EXAMPLES 9A & 9B



Example 9A



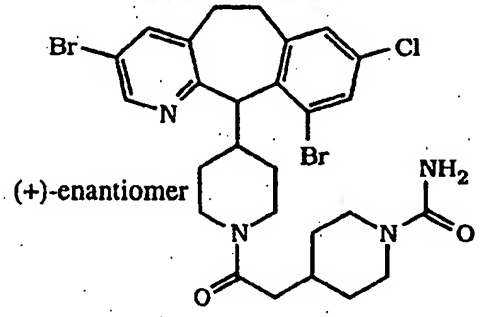
Example 9B

The (-)-enantiomer of the title compound of Preparative Example 8, Step B, (3.38 g) is reacted with 2.20 g of the title compound of Preparative Example 1, via substantially the same procedure as described for Example 9 to give 3.58 g of the title compound of Example 9A.

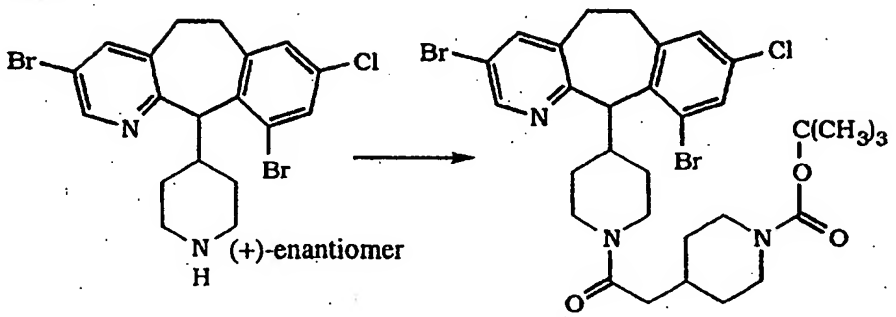
The HCl salt of the title compound of Example 9A is prepared by dissolving of the title compound in CH_2Cl_2, adding 6M HCl (g) in CH_2Cl_2, then concentrating *in vacuo* to give the salt. m.p. = 129°C; $[\alpha]_D^{25}$ = -72.3° (3.32mg/2mL MeOH).

The racemic title compound of Preparative Example 8, Step A, is reacted with the title compound of Preparative Example 1, via substantially the same procedure as described for Example 9 to give the title compound of Example 9B. m.p. = 145.0°C.

EXAMPLE 10



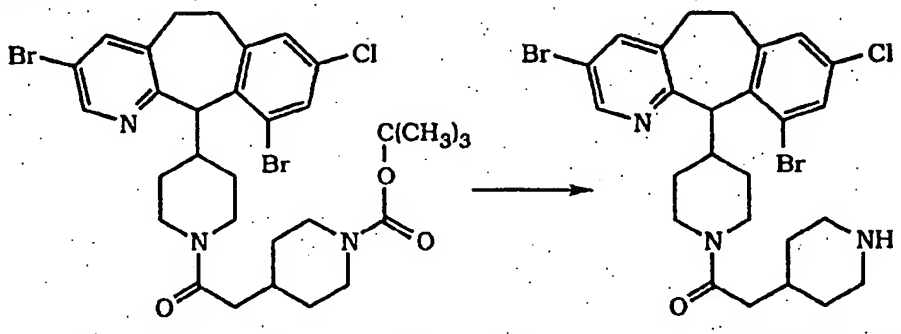
Step A:



React 1.33 g of the (+)-enantiomer of the title compound of Preparative Example 8, Step B, with 1.37 g of 1-N-t-butoxy-carbonylpiperidinyl-4-acetic acid using substantially the same procedures as described for Example 6, Step A, to give 2.78 g of

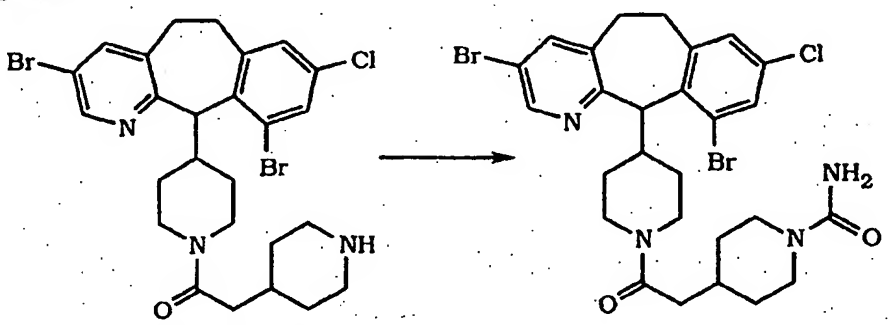
the product. Mass Spec.: MH^+ = 694.0 (FAB); $[\alpha]_D^{25}$ = +34.1° (5.45 mg/2 mL, MeOH).

Step B:



Treat 2.78 g of the product of Step A via substantially the same procedure as described for Example 8, Step B, to give 1.72 g of the product. m.p. = 104.1°C; Mass Spec.: MH^+ = 594; $[\alpha]_D^{25}$ = +53.4° (11.42 mg/2 mL, MeOH).

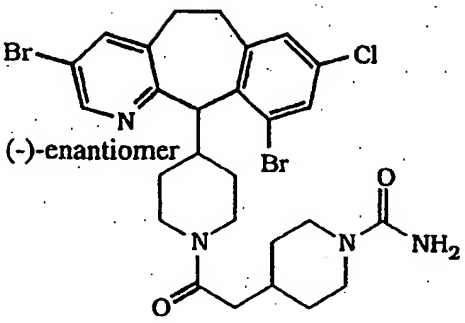
Step C:



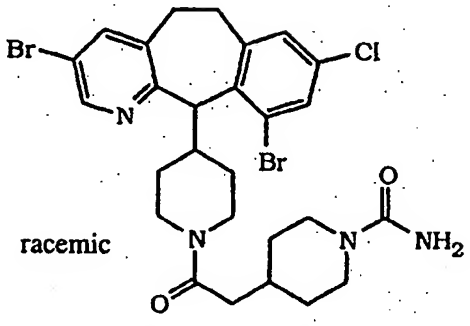
Treat 1.58 g of the product of Step B with 6 mL of $(CH_3)_3SiNCO$ using substantially the same procedure as described for Example 6, Step C, to give 1.40 g of the title compound. m.p. = 140°C; Mass spec.: MH^+ = 637; $[\alpha]_D^{25}$ = +49.1° (4.24mg/2 mL, MeOH).

Recrystallization from acetone provided the title compound as a solid. m.p. = 214.5-215.9°C.

EXAMPLES 10A & 10B



Example 10A

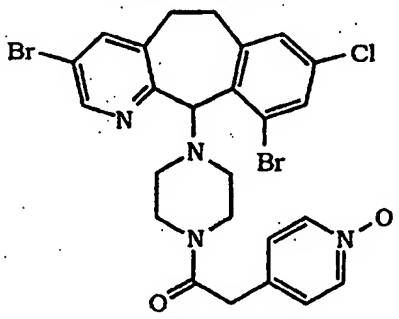


Example 10B

The (-)-enantiomer of the title compound of Preparative Example 8, Step B, (3.38 g) is converted to the title compound (Example 10A) via substantially the same procedure as described for Example 10, Steps A-C, to give the title compound Example 10A. m.p. = 152°C; Mass spec.: $MH^+ = 637$; $[\alpha]_D^{25} = -62.5°$ (1,12mg/2mL MeOH).

The racemic title compound of Preparative Example 8, Step A, is converted to the title compound (Example 9B) via substantially the same procedure as described for Example 10, Steps A-C to give the title compound Example 10B. m.p. = 111.2°C (dec).

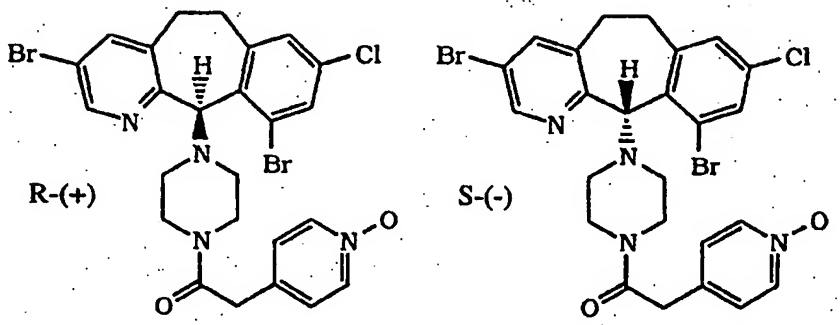
Example 11



The title compound is prepared using the racemic title compound from Preparative Example 9, Step F, following substantially the same procedure as described for Example 2. ^1H NMR ($CDCl_3$, 400 MHz): 8.44 (d, 1H); 8.14 (d, 2H): 7.58 (d, 1H); 7.47 (d, 1H); 7.14 (m, 3H); 5.32 (s, 1H); 4.65-4.57 (m, 1H);

3.68 (s, 2H); 3.65-3.39 (m, 4H); 2.91-2.87 (m, 1H); 2.69-2.63 (m, 1H); 2.45-2.33 (m, 4H). MH^+ = 605.

Example 11A & 11B



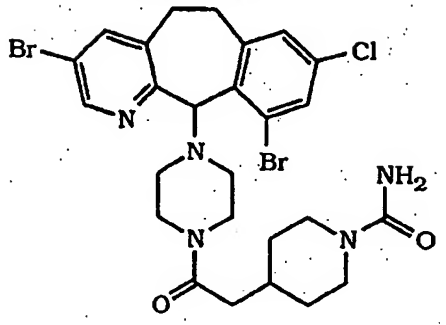
Example 11A Example 11B

Using the R(+)- or S(-)-enantiomer of the title compound from Preparative Example 9, Step G, the R(+)-enantiomer (Example 11A) or the S-(-)-enantiomer (Example 11B) is prepared using substantially the same procedure as described for Example 2.

Physical chemical data for R-(+)-enantiomer, Example 11A: m.p. = 167.0°-167.8°C; $[\alpha]_D^{25}$ = +32.6° (c = 1, MeOH); ^1H NMR ($CDCl_3$, 400 MHz): 8.44 (d, 1H); 8.14 (d, 2H): 7.58 (d, 1H); 7.47 (d, 1H); 7.14 (m, 3H); 5.32 (s, 1H); 4.65-4.57 (m, 1H); 3.68 (s, 2H); 3.65-3.39 (m, 4H); 2.91-2.87 (m, 1H); 2.69-2.63 (m, 1H); 2.45-2.33 (m, 4H). MH^+ = 605.

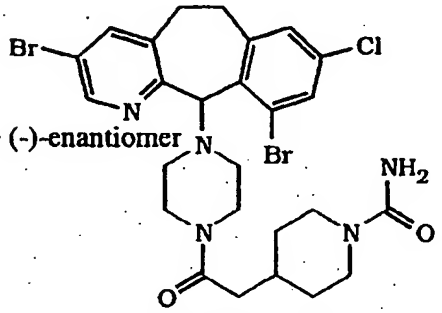
Physical chemical data for S-(-)-enantiomer, Example 11B: $[\alpha]_D^{25}$ = -38.2° (14.67 mg/2 mL, MeOH); ^1H NMR ($CDCl_3$, 400 MHz): 8.44 (d, 1H); 8.14 (d, 2H): 7.58 (d, 1H); 7.47 (d, 1H); 7.14 (m, 3H); 5.32 (s, 1H); 4.64-4.57 (m, 1H); 3.67 (s, 2H); 3.70-3.34 (m, 4H); 2.95-2.87 (m, 1H); 2.69-2.63 (m, 1H); 2.45-2.31 (m, 4H). MH^+ = 605.

Example 12

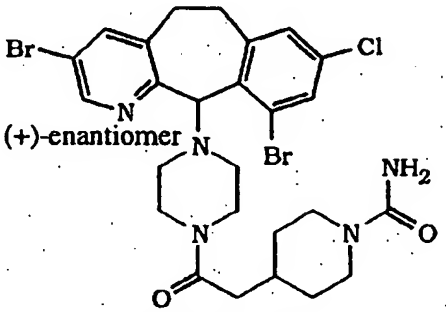


The title compound of this Example is prepared using the racemic title compound from Preparative Example 9, Step F, by following substantially the same procedures as described for Example 8, Steps A-C. This compound is a racemate.

EXAMPLES 12A & 12B



Example 12A



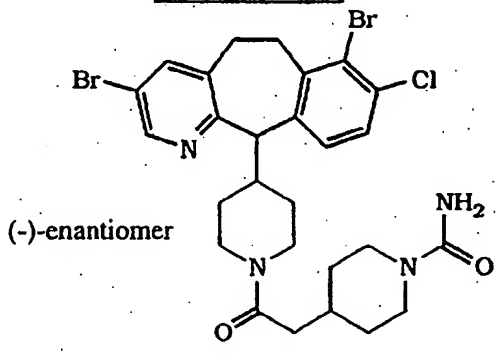
Example 12B

The title compound of Example 12 is a racemic mixture. Chromatograph 2.45 g of the compound of Example 12, using an Chiralpack AD column and 20% i-PrOH/ hexane + 0.2% diethylamine as the mobile phase, at a flow rate of 100 mL/min., to give 0.970 g of the (+)-enantiomer and 0.982 g of the (-)-enantiomer, Examples 12B and 12A, respectively.

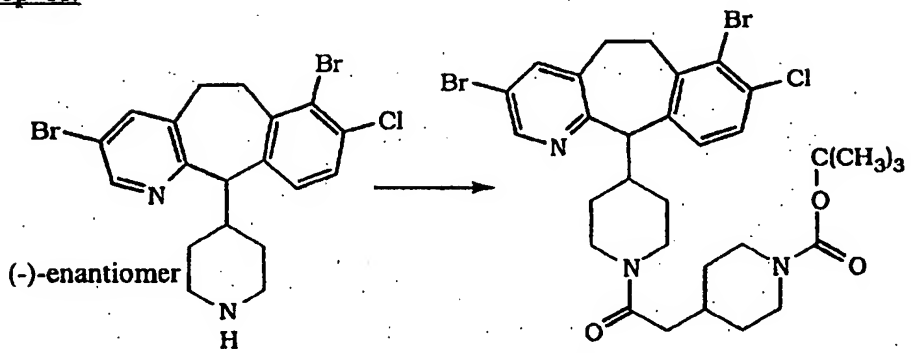
Physical chemical data for (-)-enantiomer, Example 12A: ^{1}H NMR ($CDCl_3$, 200 MHz): 8.43 (d, 1H); 7.58 (d, 1H); 7.48 (d, 1H); 7.14 (d, 1H); 5.32 (s, 1H); 4.5-4.75 (m, 1H); 4.4 (s, 2H); 3.9 (d, 2H); 3.2-3.7 (m, 5H); 2.52-3.05 (m, 4H); 1.85-2.5 (m, 6H); 1.5-1.85 (m, 4H); 1.0-1.4 (m, 1H). $[\alpha]_D^{25}$ = -31.2° (c = 0.453, MeOH).

Physical chemical data for (+)-enantiomer, Example 12B: ^{1}H NMR ($CDCl_3$, 200 MHz): 8.43 (d, 1H); 7.58 (d, 1H); 7.48 (d, 1H); 7.14 (d, 1H); 5.32 (s, 1H); 4.5-4.75 (m, 1H); 4.4 (s, 2H); 3.9 (d, 2H); 3.2-3.7 (m, 5H); 2.52-3.05 (m, 4H); 1.85-2.5 (m, 6H); 1.5-1.85 (m, 4H); 1.0-1.4 (m, 1H). $[\alpha]_D^{25}$ = +29.8° (c = 0.414, MeOH).

EXAMPLE 13

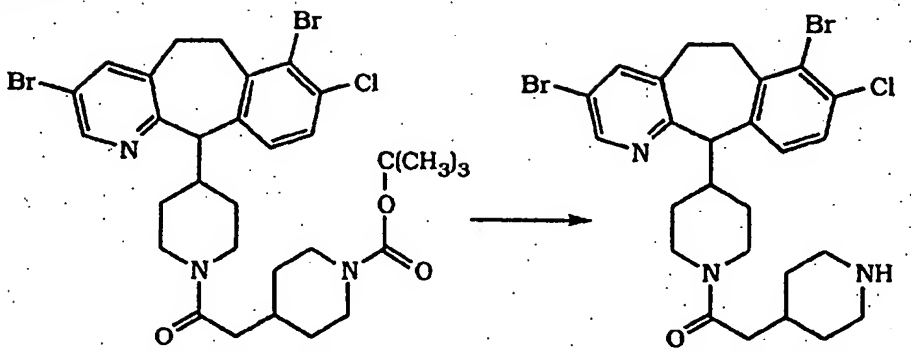


Step A:



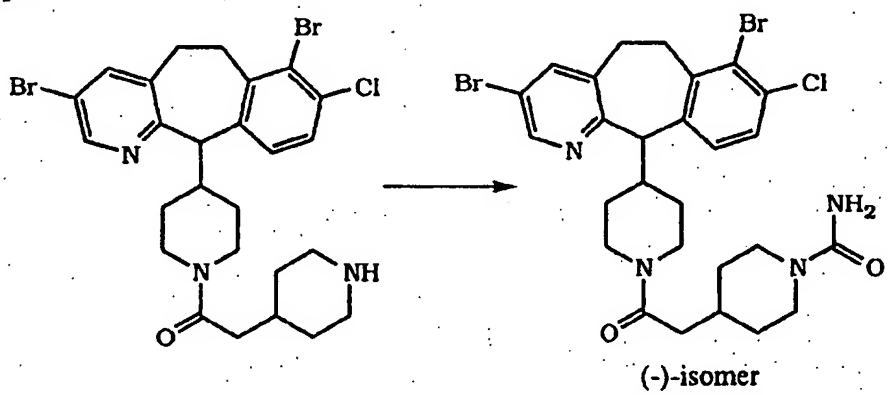
React 1.35 g of the (-)-enantiomer of the title compound of Preparative Example 10, Step B, with 1.4 g of 1-N-t-butoxy-carbonylpiperidinyl-4-acetic acid following substantially the same procedures as described for Example 6, Step A, to give 2.0 g of the product. Mass Spec.: MH^+ = 694 (FAB). partial ^{1}H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1H); 7.60 (s, 1H); 7.25 (d, 1H); 7.05 (m, 1H); 1.45 (s, 9H).

Step B:



Treat 1.95 g of the product of Step A via substantially the same procedure as described for Example 8, Step B, to give 1.63 g of the product. Mass Spec. MH^+ = 594 (FAB). Partial ^1H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1H); 7.60 (s, 1H); 7.25 (d, 1H); 7.03 (m, 1H); 4.64 (d, 1H); 3.90 (m, 2H).

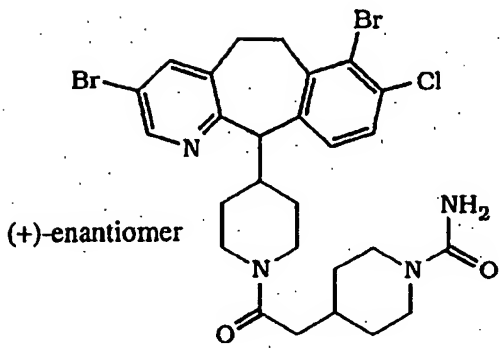
Step C:



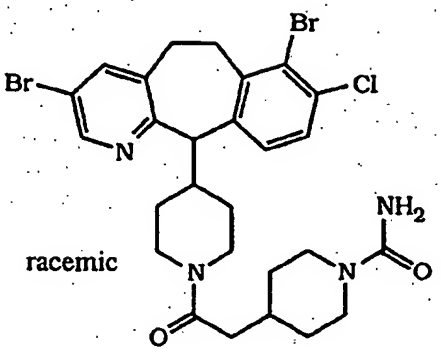
(-)-isomer

Treat 1.6 g of the product of Step B with 1.3 mL of $(CH_3)_3SiNCO$ using substantially the same procedure as described for Example 6, Step C, to give 1.27 g of the title compound. Mass spec.: MH^+ = 637 (FABS); $[\alpha]_D^{25}$ = -33.1° (c=0.58, EtOH). partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.59 (s, 1H); 7.25 (d, 1H); 7.04 (m, 1H); 4.60 (d, 1H); 4.41 (s, 2H).

EXAMPLES 13A & 13B



Example 13A

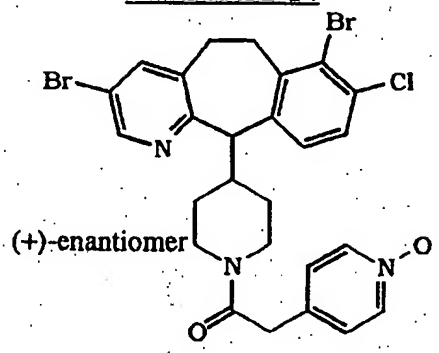


Example 13B

The (+)-enantiomer of the title compound from Preparative Example 10, Step B, (2.1 g) is converted to the title compound via substantially the same procedure as described for Example 10, Steps A-C, to give the title compound, Example 13A. Mass spec.: $MH^+ = 637$ (FABS); $[\alpha]_D^{25} = +32.4°$ (c=0.57, EtOH). Partial ^1H NMR ($CDCl_3$, 400 MHz): 8.39 (s, 1H); 7.59 (s, 1H); 7.25 (d, 1H); 7.04 (m, 1H); 4.60 (d, 1H); 4.41 (s, 2H). partial ^1H NMR (DMSO-d_6, 400 MHz): 8.42 (s, 1H); 7.88 (s, 1H); 7.41 (d, 1H); 7.29 (m, 1H); 5.85 (s, 2H); 4.20 (d, 1H).

The racemic title compound from Preparative Example 10, Step A, is converted to the racemic title compound, Example 13B, in an analogous manner. Partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.59 (s, 1H); 7.25 (d, 1H); 7.04 (m, 1H); 4.60 (d, 1H); 4.41 (s, 2H). partial ^1H NMR (DMSO-d_6, 400 MHz): 8.42 (s, 1H); 7.88 (s, 1H); 7.41 (d, 1H); 7.29 (d, 1H); 5.85 (s, 2H); 4.20 (d, 1H).

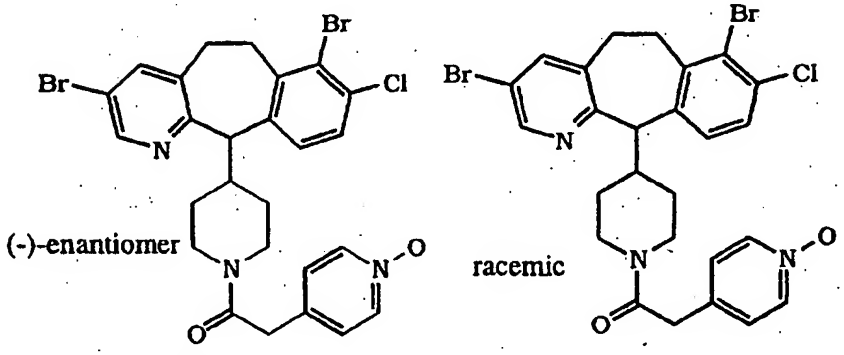
EXAMPLE 14



React 2.6 g of the (+)-enantiomer of the title compound of Preparative Example 10, Step B, and 1.68 g of the title compound of Preparative Example 1 following substantially the same procedure as described for Example 9 to give 2.10 g of the title compound. Mass spec.: $MH^+ = 604$ (FAB); $[\alpha]_D^{25} = +34.1°$ (10.98 mg/2 mL, EtOH). partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 8.15 (d, 2H); 7.58 (s, 1H); 7.26 (d, 1H); 7.15 (d, 2H); 7.03 (d, 1H); 4.57 (d, 1H).

To prepare the HCl salt of the title compound of Example 14 dissolve 700 mg of the title compound in 4 mL of CH_2Cl_2, add 4 mL of Et_2O, cool to 0°C and slowly add (dropwise) 1 mL of HCl (g) in dioxane. Add 2 mL of Et_2O and stir at 0°C for 7 min. Dilute with 30 mL of Et_2O, filter to collect the solid product and wash with 30 mL of Et_2O. Dry the solids *in vacuo* to give 0.836 g of the HCl salt of Example 14. $[\alpha]_D^{25} = +64.8°$ (9.94 mg/2 mL, EtOH).

EXAMPLE 14A & 14B



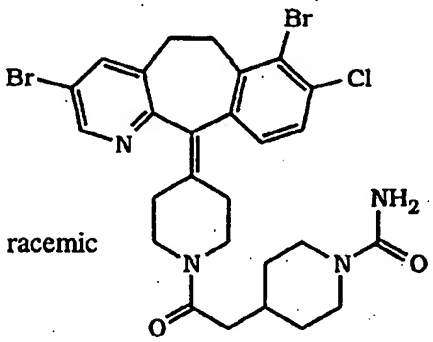
Example 14A Example 14B

The (-)-enantiomer of the title compound of Preparative Example 10, Step B, (0.60 g) is reacted with 0.39 g of the title compound of Preparative Example 1, via substantially the same procedure as described for Example 9 to give 0.705 g of the title compound. Mass spec.: $MH^+ = 604$ (FABS); $[\alpha]_D^{25} = -41.8°$ (EtOH). Partial ^1H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1H); 8.15 (d, 2H); 7.58 (s, 1H); 7.26 (d, 1H); 7.15 (d, 2H); 7.03 (d, 1H); 4.57 (d, 1H).

The HCl salt of the title compound of Example 14A is prepared via substantially the same procedure as described for Example 14. $[\alpha]_D^{25}$ = -63.2° (EtOH).

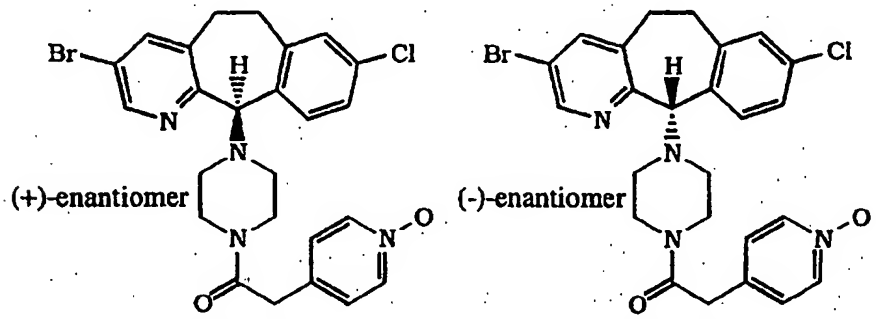
The racemic title compound of Preparative Example 10, Step A, is converted to the racemic title compound of Example 14B following substantially the same procedure as described for Example 9. Partial ^{1}H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 8.15 (d, 2H); 7.58 (s, 1H); 7.26 (d, 1H); 7.15 (d, 2H); 7.03 (d, 1H); 4.57 (d, 1H). Partial ^{1}H NMR (DMSO-d_6, 400 MHz): 8.77 (d, 2H); 8.47 (s, 1H); 7.95 (s, 1H); 7.74 (d, 2H); 7.43 (m, 1H); 7.27 (d, 1H); 4.35 (d, 1H).

EXAMPLE 15



The title compound of Preparative Example 4 is reacted via substantially the same methods as described for Example 8, Steps A-C, to give the title compound, which is a racemate. Mass Spec.: MH^+ = 635 (FAB). Partial ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H); 7.60 (s, 1H); 7.35 (d, 1H); 7.05 (d, 1H); 4.45 (s, 1H).

Example 16A & 16B



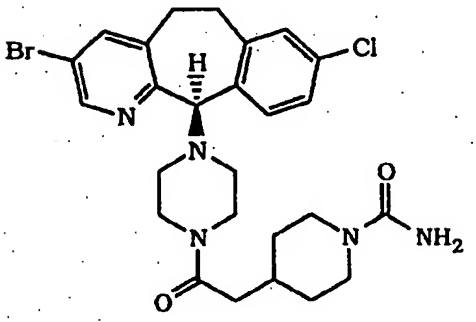
Example 16A Example 16B

The R-(+)-enantiomer or the S-(-) enantiomer of the title comound of Preparative Example 11 is treated via substantially the same procedure as described for Example 2 to give the R-(+)-enantiomer of the title compound or the S-(-)-enantiomer of the title compound, Examples 16A and 16B, respectively.

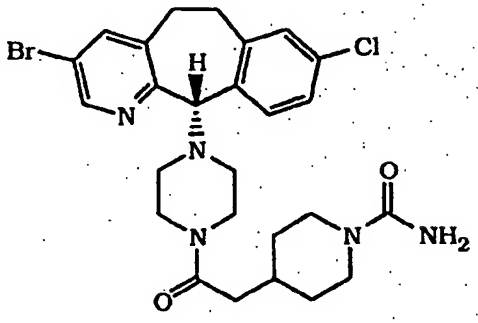
Physical chemical data for the R-(+)-enantiomer: ^{13}C NMR ($CDCl_3$): 166.5 (C); 154.8 (C); 146.6 (CH); 140.8 (CH); 140.4 (C); 138.5 (CH); 138.5 (CH); 136.3 (C); 134.6 (C); 133.8 (C); 133.6 (C); 132.0 (CH); 130.0 (CH); 126.3 (CH); 126.3 (CH); 125.8 (CH); 119.6 (C); 78.4 (CH); 51.1 (CH_2); 50.6 (CH_2); 45.4 (CH_2); 41.5 (CH_2); 38.0 (CH_2); 30.1 (CH_2); 30.0 (CH_2). $[\alpha]_D^{25}$ = +30.7° (10.35 mg/2 mL MeOH).

Physical chemical data for the S-(-)-enantiomer: ^{13}C NMR ($CDCl_3$): 166.5 (C); 154.8 (C); 146.6 (CH); 140.8 (CH); 140.4 (C); 138.5 (CH); 138.5 (CH); 136.3 (C); 134.6 (C); 133.8 (C); 133.6 (C); 132.0 (CH); 130.0 (CH); 126.3 (CH); 126.3 (CH); 125.8 (CH); 119.6 (C); 78.4 (CH); 51.1 (CH_2); 50.6 (CH_2); 45.4 (CH_2); 41.5 (CH_2); 38.0 (CH_2); 30.1 (CH_2); 29.9 (CH_2). $[\alpha]_D^{25}$ = -30.9° (9.70 mg/2 mL MeOH).

Examples 17 & 17A



Example 17



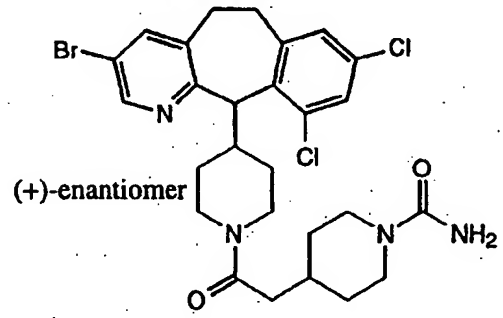
Example 17A

Treat the (+)-enantiomer or the (-)-enantiomer of the title compound of Preparative Example 11 via substantially the same procedure as described for Example 1, Steps A-C, to give the R-(+)-enantiomer of the title compound or the S-(-)-enantiomer of the title compound, Examples 17 and 17A, respectively.

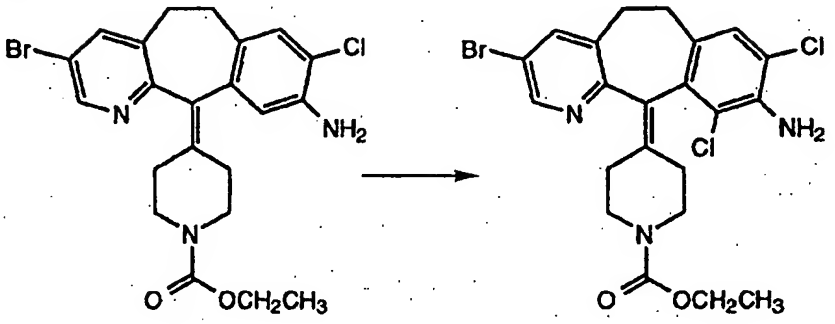
Physical chemical data for the R-(+)-enantiomer: ^{13}C NMR ($CDCl_3$): 169.3 (C); 157.5 (C); 155.0 (C); 146.6 (CH); 140.8 (CH); 140.4 (C); 136.3 (C); 134.8 (C); 133.7 (C); 132.0 (CH); 130.0 (CH); 125.8 (CH); 119.6 (C); 78.5 (CH); 51.4 (CH_2); 50.9 (CH_2); 45.2 (CH_2); 43.9 (CH_2); 43.9 (CH_2); 41.1 (CH_2); 38.8 (CH_2); 32.5 (CH); 31.5 (CH_2); 31.5 (CH_2); 30.1 (CH_2); 30.0 (CH_2). $[\alpha]_D^{24.8}$ = +28.7° (10.1 mg/2 mL MeOH).

Physical chemical data for the S-(-)-enantiomer: ^{13}C NMR ($CDCl_3$): 169.3 (C); 157.6 (C); 155.0 (C); 146.6 (CH); 140.8 (CH); 140.4 (C); 136.3 (C); 134.8 (C); 133.7 (C); 132.0 (CH); 130.0 (CH); 125.8 (CH); 119.6 (C); 78.5 (CH); 51.4 (CH_2); 50.9 (CH_2); 45.2 (CH_2); 43.9 (CH_2); 43.9 (CH_2); 41.1 (CH_2); 38.8 (CH_2); 32.5 (CH); 31.5 (CH_2); 31.5 (CH_2); 30.1 (CH_2); 30.0 (CH_2). $[\alpha]_D^{24.8}$ = -28.5° (10.1 mg/2 mL MeOH).

EXAMPLE 18



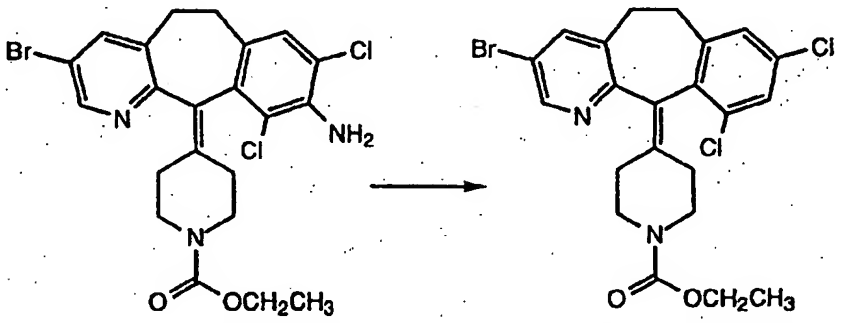
Step A:



Dissolve 9.90 g (18.9 mmol) of the product of Preparative Example 7, Step B, in 150 mL CH_2Cl_2 and 200 mL of CH_3CN and heat to 60°C. Add 2.77 g (20.8 mmol) N-chlorosuccinimide and heat to reflux for 3 h., monitoring the reaction by TCL

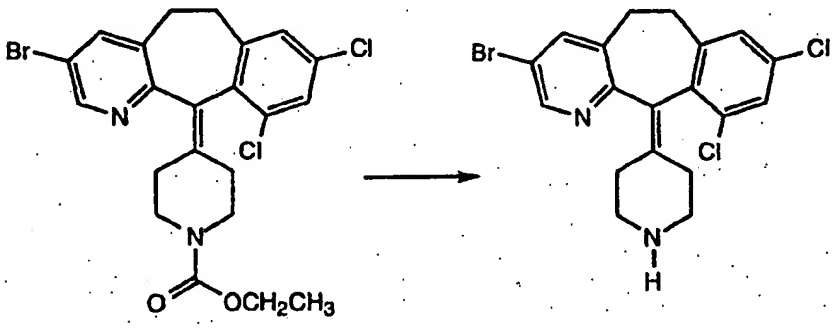
(30%EtOAc/H_2O). Add an additional 2.35 g (10.4 mmol) of N-chlorosuccinimide and reflux an additional 45 min. Cool the reaction mixture to room temperature and extract with 1N NaOH and CH_2Cl_2. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and purify by flash chromatography (1200 mL normal phase silica gel, eluting with 30% EtOAc/H_2O) to obtain 6.24 g of the desired product. M.p. 193-195.4°C. MH^+ = 510.

Step B:



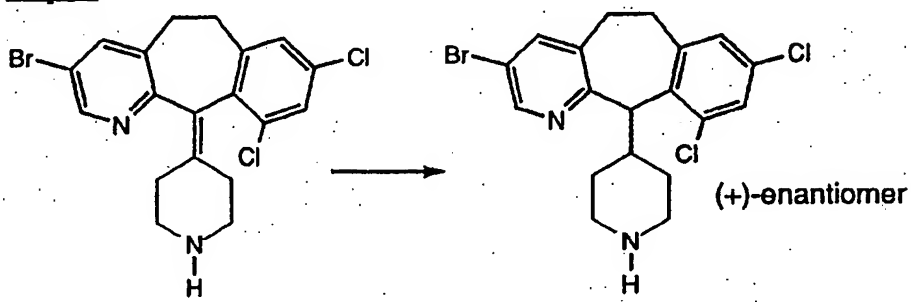
To 160 mL of conc. HCl at -10°C add 2.07 g (30.1 mmol) $NaNO_2$ and stir for 10 min. Add 5.18 g (10.1 mmol) of the product of Step A and warm the reaction mixture from -10°C to 0°C for 2 h. Cool the reaction to -10°C, add 100 mL H_3PO_2 and let stand overnight. To extract the reaction mixture, pour over crushed ice and basify with 50% NaOH/ CH_2Cl_2. Dry the organic layer over $MgSO_4$, filter and concentrate to dryness. Purify by flash chromatography (600 mL normal phase silica gel, eluting with 20% EtOAc/hexane) to obtain 3.98 g of product. Mass spec.: MH^+=495.

Step C:



Dissolve 3.9 g of the product of Step B in 100 mL conc. HCl and reflux overnight. Cool the mixture, basify with 50 % w/w NaOH and extract the resultant mixture with CH_2Cl_2. Dry the CH_2Cl_2 layer over $MgSO_4$, evaporate the solvent and dry under vacuum to obtain 3.09 g of the desired product. Mass spec.: MH^+=423.

Step D:

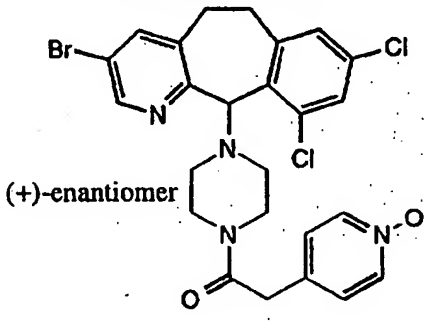


Using a procedure similar to that described in Preparative Example 8, obtain 1.73 g of the desired product, m.p. 169.6-170.1°C; $[\alpha]_D^{25}$ = +48.2° (c=1, MeOH). MH^+ = 425.

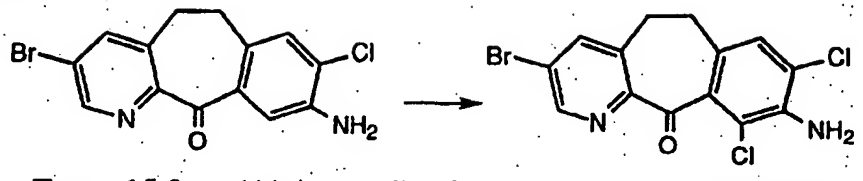
Step E:

Use a procedure similar to that of Example 4 with the product of Step D as the starting material to obtain the title compound. M.p. 152.3-153.3°C; $[\alpha]_D^{25}$ = +53.0° (c=1, MeOH). MH^+ = 593.

EXAMPLE 19

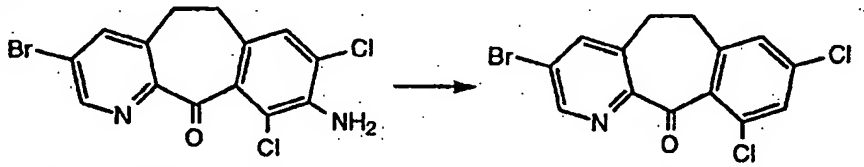


Step A:



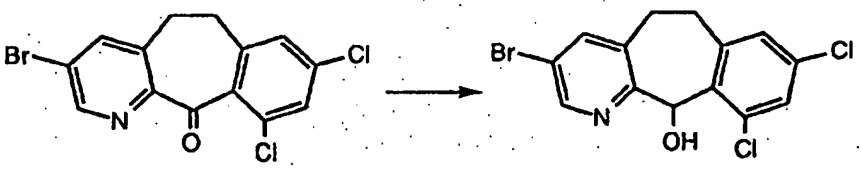
Treat 15.0 g (44.4 mmol) of the product of Preparative Example 9, Step B, with 6.52 g (48.9 mmol) of N-chloro-succinimide in a manner similar to that described in Example 18, Step A and extract as described to obtain 16.56 g of the desired product, m.p. 234.7-235.0°C. MH^+ = 370.

Step B:



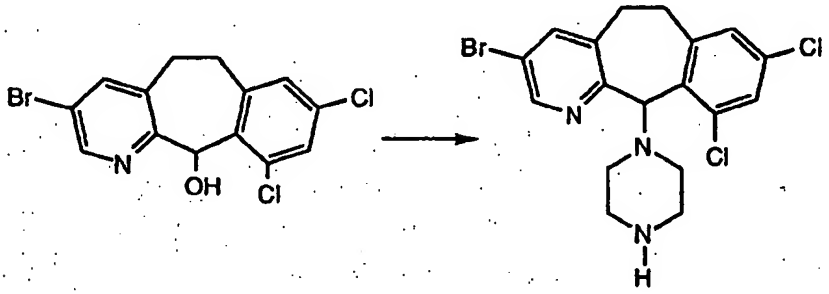
Treat 16.95 g (45.6 mmol) of the product of Step A in the manner described in Example 18, Step B, to obtain 13.07 g of the desired product, m.p. 191.7-192.1°C. MH^+ = 356.

Step C:



Using the procedure substantially as described in Preparative Example 9, Step E, treat 10.0 g (28.0 mmol) of the product of Step B with $NaBH_4$ to obtain the desired product, which is used in the next step without further purification.

Step D:

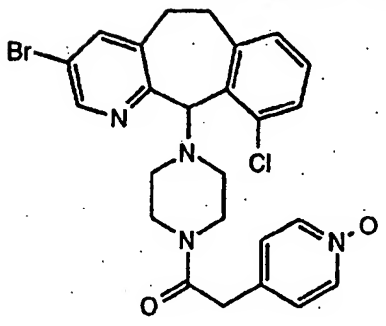


Dissolve 10.0 g (27.9 mmol) of the product of Step C in 200 mL CH_2Cl_2 under N_2 with stirring at room temperature. Cool the reaction mixture to 0°C and add 2.63 g of triethylamine and 4.80 g (41.9 mmol) of methanesulfonyl chloride. To the resultant solution at 0°C add a solution of 16.84 g (19.6 mmol) piperazine and 100 mL of THF, immediately followed by 100 mL DMF. Stir overnight at room temperature. Evaporate the solvent and extract the resultant residue with CH_2Cl_2 and sat'd $NaHCO_3$. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and concentrate to obtain the crude product. Chromatograph the crude product on 1200 mL silica gel, eluting with 5% CH_3OH(sat'd with NH_3) in CH_2Cl_2 to obtain a racemic mixture. Separate the racemic compound by chiral chromatography using a Chiralpack AD column (5 cm x 50 cm), eluting with 30% iPrOH/hexane with 0.2% diethylamine. Mass spec.: MH^+=426. The desired isomer is the (+)-enantiomer.

Step E:

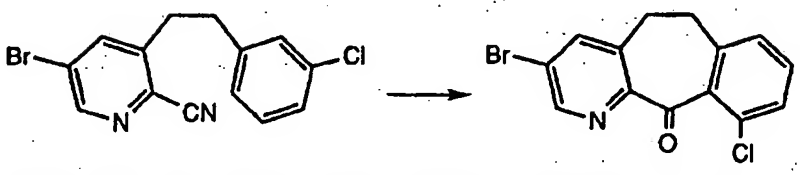
Stir 2.0 g (4.7 mmol) of the product of Step D in 40 mL DMF under N_2, cool the mixture to 0° and add 0.615 g (6.1 mmol) N-methylmorpholine, 1.1668 g (6.1 mmol) DEC, 0.8225 g (6.1 mmol) HOBT and 1.6042 g (6.1 mmol) of the product of Preparative Example 1. Stir overnight at room temperature. Evaporate the solvent and extract the resultant residue with CH_2Cl_2/water, sat'd $NaHCO_3$, 10% NaH_2PO_4 and brine. Separate the CH_2Cl_2 layer, dry over $MgSO_4$, filter and concentrate to dryness. Purify the resultant residue by flash chromatography on 400 mL of normal phase silica gel, eluting with 5% CH_3OH/NH_3-CH_2Cl_2 to obtain 2.43 g of the title compound, m.p. 145.3-146.1°C; $[\alpha]_D^{25}$ = +33.6° (c=1, MeOH). MH^+ = 561.

EXAMPLE 20



(+)-enantiomer

Step A:

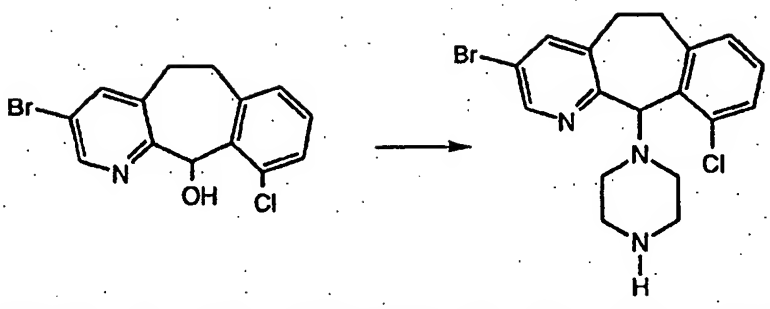


Heat 200 mg of the cyano starting material in 17 g polyphosphoric acid at 190-200°C for 45 min. Pour the resultant mixture into ice, add 30% HCl and stir for 30 min. Extract with CH_2Cl_2, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify by preparative TLC, eluting with EtOAc/hexane to obtain 21 mg of the desired product (also obtained 59 mg of the 10-chloro product).

Step B:

Using the procedure substantially as described in Preparative Example 9, Step E, treat 1.75 g (5.425 mmol) of the product of Step A with $NaBH_4$ to obtain the desired product.

Step C:

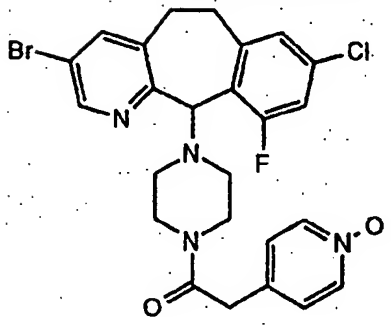


Dissolve the residue obtained in Step B in 50 mL CH_2Cl_2 at room temperature, add 3.95 mL (5.425 mmol) of $SOCl_2$ and stir at room temperature overnight. Remove excess $SOCl_2$ and solvent under vacuum. Dissolve the residue in CH_2Cl_2, wash with sat'd $NaHCO_3$ and brine, dry over Na_2SO_4, filter and concentrate. Add 25 mL THF to the resultant residue, add 2.33 g (27.125 mmol) piperazine and stir at room temperature overnight. Evaporate the solvent, add CH_2Cl_2 wash with sat'd $NaHCO_3$ and brine, dry over Na_2SO_4, filter and concentrate. Purify the resultant residue by chiral chromatography using a Chiralpack AD column and eluting with 20% iPrOH/hexane with 0.2% diethylamine. Mass spec.: MH^+=392. The desired isomer is the (+)-enantiomer.

Step D:

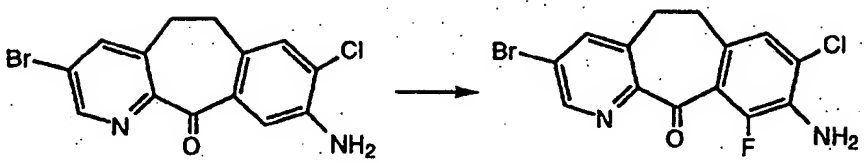
Combine 770 mg (1.960 mmol) of the product of Step C, 323µl (2.548 mmol) N-methylmorpholine, 344 mg (2.548 mmol) HOBT, 487 mg (2.548 mmol) DEC and 390 mg (2.548 mmol) of the compound of Preparative Example 1 in 8 ml DMF and stir at room temperature overnight. Evaporate the solvent, add EtOAc and wash with sat'd $NaHCO_3$, water and brine, and dry over Na_2SO_4. Purify by flash chromatography on silica gel, eluting with EtOAc to 10, 12% (10%NH_4OH/CH_3OH)/EtOAc gradient. Further purify by preparative TLC (1000µ silica gel) to obtain 750 mg of the title compound, $[\alpha]_D^{25}$ = +23.3° (c=0.322, MeOH).

EXAMPLE 21



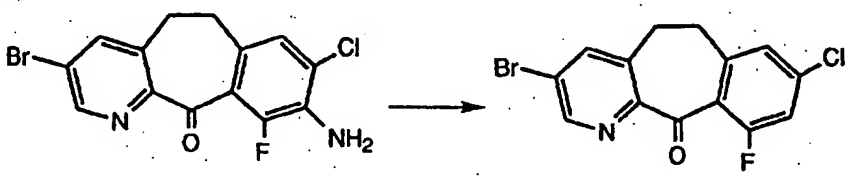
racemic

Step A:



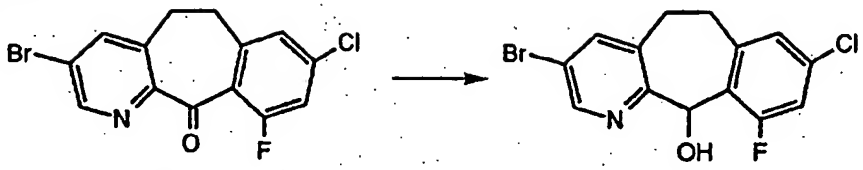
Dissolve 10.0 g (29.6mmol) of the product of Preparative Example 9, Step B, in 150 mL CH_2Cl_2 and 200 mL CH_3CN at room temperature. Heat the mixture to 60°C, add 10.45 g (32.6 mmol) of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2,2,2]octane bis-(tetrafluoroborate) and heat to reflux for 4 h. Cool the mixture to room temperature, extract with CH_2Cl_2 and 1 N NaOH. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and concentrate to dryness. Purify the resultant residue by flash chromatography using 1400 mL normal phase silica gel eluted with 10% EtOAc-CH_2Cl_2 + 2 drops NH_4OH to obtain 2.00 g of product, m.p. 103.2-103.5°C. MH^+ = 355.

Step B:



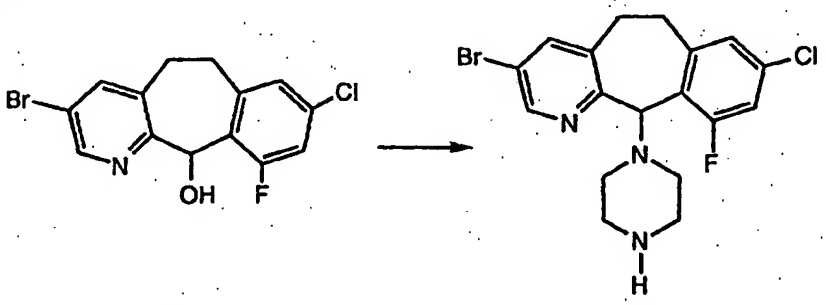
Using a procedure substantially as described in Preparative Example 9, Step D, treat 1.80 g (5.1 mmol) of the product of Step A. Purify the crude product by flash chromatography using 200 mL normal phase silica gel eluted with 20% EtOAc/hexane. Mass spec.: MH^+ = 339.

Step C:



Using the procedure substantially as described in Preparative Example 9, Step E, treat 0.47 g (1.4 mmol) of the product of Step B with $NaBH_4$ to obtain the desired product. Mass spec.: MH^+=342.

Step D:



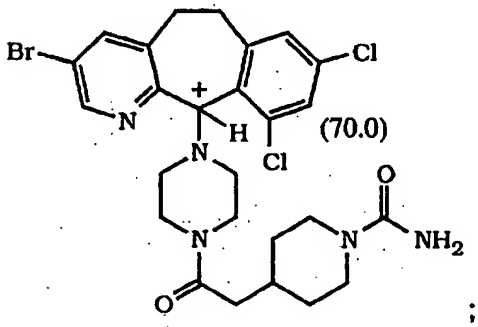
Dissolve 0.37 g (1.1 mmol) of the product of Step C in 20 mL toluene under N_2 and cool from room temperature to 0°C. Add 0.3855 g (3.2 mmol) of $SOCl_2$ and stir at room temperature, then add 10 mL $CHCl_3$ and stir for 3 h. Evaporate the solvent, extract the resultant residue with 1 N NaOH-CH_2Cl_2, dry the CH_2Cl_2 layer over $MgSO_4$, filter and concentrate to dryness. Dissolve the residue in 10 mL THF under N_2, add 0.465 g (5.4 mmol) of piperazine, 10 mL THF and stir overnight at room temperature. Repeat the extraction procedure to obtain the desired product. Mass spec.: MH^+=410.

Step E:

Treat 0.44 g (1.1 mmol) of the product of Step D with N-methylmorpholine, 4-pyridylacetic acid N-oxide, DEC and HOBT in DMF as described in Example 5. Evaporate the solvent and extract the resultant residue with CH_2Cl_2-H_2O, sat'd $NaHCO_3$, 10% NaH_2PO_4 and brine. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and concentrate to dryness. Purify the resultant residue by flash chromatography on 150 mL normal phase silica gel, eluting with

5% CH_3OH/NH_3-CH_2Cl_2 to obtain 0.41 g of the title compound, m.p. 155.0-155.6°C; Mass spec.: MH^+=545.

Using appropriate starting materials and procedures as described above, the following compounds could be made:



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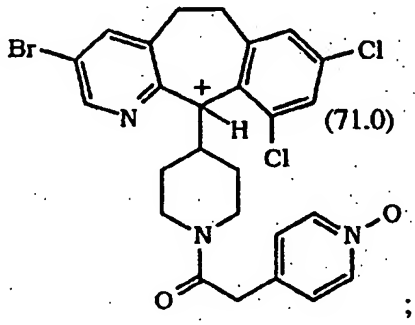

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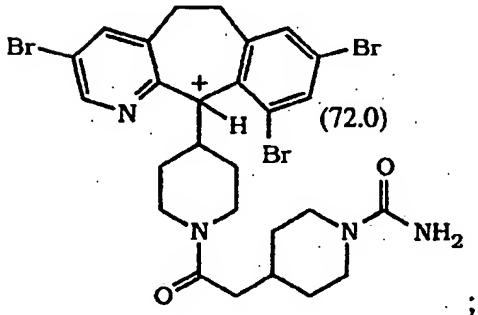

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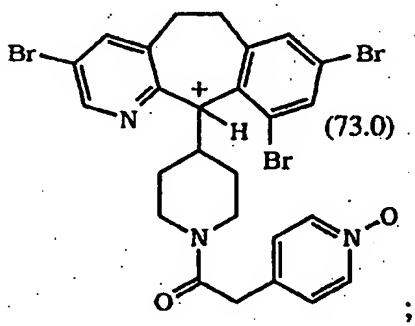

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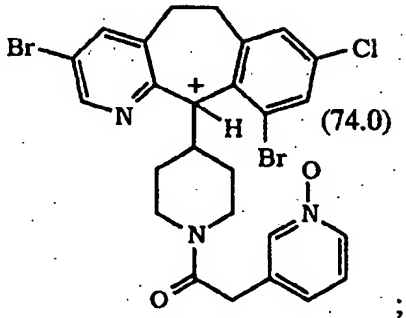

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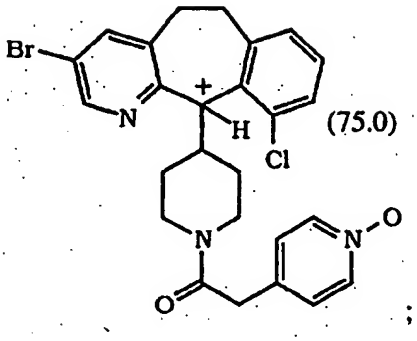
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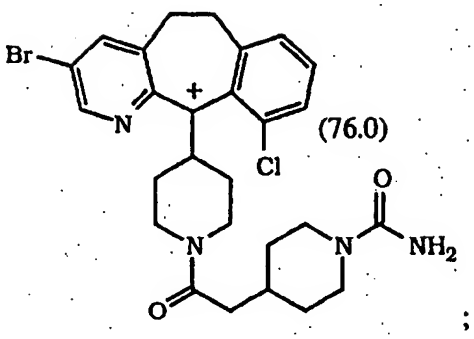
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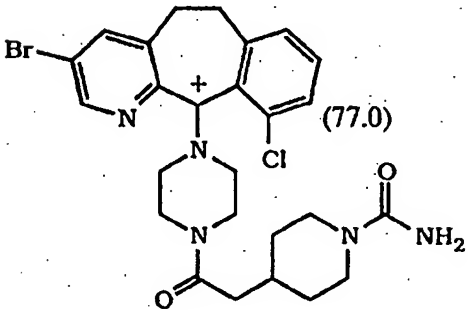
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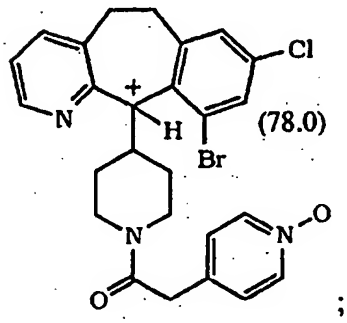
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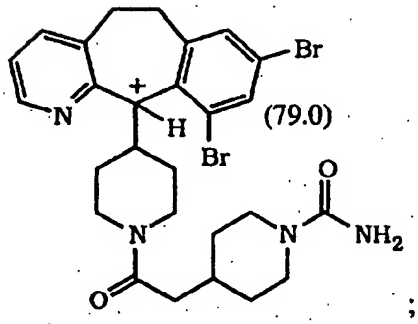
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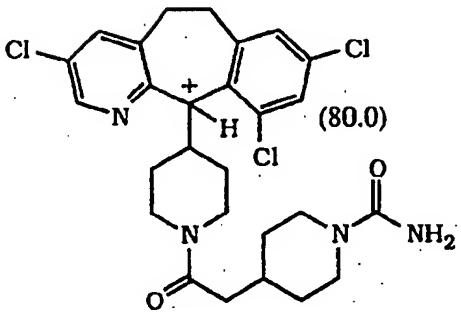
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ASSAYS

1. In vitro enzyme assays: Inhibition of farnesyl protein transferase and geranylgeranyl protein transferase.

Both farnesyl protein transferase (FPT) and geranylgeranyl protein transferase (GGPT) I were partially purified from rat brain by ammonium sulfate fractionation followed by Q-Sepharose (Pharmacia, Inc.) anion exchange chromatography essentially as described by Yokoyama et al (Yokoyama, K., et al., (1991), A protein geranylgeranyltransferase from bovine brain: Implications for protein prenylation specificity, **Proc. Natl. Acad. Sci USA 88: 5302-5306**, the disclosure of which is incorporated herein by

reference thereto). Human farnesyl protein transferase was also expressed in E. coli, using cDNA clones encoding both the a and b subunits. The methods used were similar to those published (Omer, C. et al., (1993), Characterization of recombinant human farnesyl protein transferase: Cloning, expression, farnesyl diphosphate binding, and functional homology with yeast prenyl-protein transferases, Biochemistry 32:5167-5176). Human farnesyl protein transferase was partially-purified from the soluble protein fraction of E. coli as described above. The tricyclic farnesyl protein transferase inhibitors disclosed herein inhibited both human and rat enzyme with similar potencies. Two forms of val^{12}-Ha-Ras protein were prepared as substrates for these enzymes, differing in their carboxy terminal sequence. One form terminated in cysteine-valine-leucine-serine (Ras-CVLS) the other in cystein-valine-leucine-leucine (Ras-CVLL). Ras-CVLS is a substrate for the farnesyl protein transferase while Ras-CVLL is a substrate for geranylgeranyl protein transferase I. The cDNAs encoding these proteins were constructed so that the proteins contain an amino-terminal extension of 6 histidine residues. Both proteins were expressed in Escherichia coli and purified using metal chelate affinity chromatography. The radiolabelled isoprenyl pyrophosphate substrates, [^{3}H]farnesyl pyrophosphate and [^{3}H]geranylgeranyl pyrophosphate, were purchased from DuPont/New England Nuclear.

Several methods for measuring farnesyl protein transferase activity have been described (Reiss et al 1990, **Cell** 62: 81; Schaber et al 1990, **J. Biol. Chem.** 265: 14701; Manne et al 1990, **PNAS** 87: 7541; and Barbacid & Manne 1993, U.S. Patent No. 5,185,248). The activity was assayed by measuring the transfer of [^{3}H]farnesyl from [^{3}H]farnesyl pyrophosphate to Ras-CVLS using conditions similar to those described by Reiss et al. 1990 (**Cell** 62: 81) The reaction mixture contained 40 mM Hepes, pH 7.5; 20 mM magnesium chloride; 5 mM dithiothreitol; 0.25 μM [^{3}H]farnesyl pyrophosphate; 10 ml Q-Sepharose-purified farnesyl protein transferase; the indicated concentration of tricyclic compound or dimethylsulfoxide (DMSO) vehicle control (5% DMSO final); and 5 mM Ras-CVLS in a

total volume of 100 ml. The reaction was allowed to proceed for 30 minutes at room temperature and then stopped with 0.5 ml of 4% sodium dodecyl sulfate (SDS) followed by 0.5 ml of cold 30% TCA. Samples were allowed to sit on ice for 45 minutes and precipitated Ras protein was then collected on GF/C filter paper mats using a Brandel cell harvester. Filter mats were washed once with 6% TCA, 2% SDS and radioactivity was measured in a Wallac 1204 Betaplate BS liquid scintillation counter. Percent inhibition was calculated relative to the DMSO vehicle control.

The geranylgeranyl protein transferase I assay was essentially identical to the farnesyl protein transferase assay described above, with two exceptions: [^{3}H]geranylgeranylpyrophosphate replaced farnesyl pyrophosphate as the isoprenoid donor and Ras-CVLL was the protein acceptor. This is similar to the assay reported by Casey et al (Casey, P.J., et al., (1991), Enzymatic modification of proteins with a geranylgeranyl isoprenoid, **Proc. Natl. Acad. Sci, USA 88: 8631-8635**, the disclosure of which is incorporated herein by reference thereto).

2. Cell-Based Assay: Transient expression of val^{12}-Ha-Ras-CVLS and val^{12}-Ha-Ras-CVLL in COS monkey kidney cells: Effect of farnesyl protein transferase inhibitors on Ras processing and on disordered cell growth induced by transforming Ras.

COS monkey kidney cells were transfected by electroporation with the plasmid pSV-SPORT (Gibco/BRL) containing a cDNA insert encoding either Ras-CVLS or Ras-CVLL, leading to transient overexpression of a Ras substrate for either farnesyl protein transferase or geranylgeranyl protein transferase I, respectively (see above).

Following electroporation, cells were plated into 6-well tissue culture dishes containing 1.5 ml of Dulbecco's-modified Eagle's media (GIBCO, Inc.) supplemented with 10% fetal calf serum and the appropriate farnesyl protein transferase inhibitors. After 24 hours, media was removed and fresh media containing the appropriate drugs was re-added.

48 hours after electroporation cells were examined under the microscope to monitor disordered cell growth induced by

transforming Ras. Cells expressing transforming Ras become more rounded and refractile and overgrow the monolayer, reminiscent of the transformed phenotype. Cells were then photographed, washed twice with 1 ml of cold phosphate-buffered saline (PBS) and removed from the dish by scraping with a rubber policeman into 1 ml of a buffer containing 25 mM Tris, pH 8.0; 1 mM ethylenediamine tetraacetic acid; 1 mM phenylmethylsulfonyl fluoride; 50 mM leupeptin; and 0.1 mM pepstatin. Cells were lysed by homogenization and cell debris was removed by centrifugation at 2000 x g for 10 min.

Cellular protein was precipitated by addition of ice-cold trichloroacetic acid and redissolved in 100 ml of SDS-electrophoresis sample buffer. Samples (5-10 ml) were loaded onto 14% polyacrylamide minigels (Novex, Inc.) and electrophoresed until the tracking dye neared the bottom of the gel. Proteins resolved on the gels were electroblotted onto nitrocellulose membranes for immunodetection.

Membranes were blocked by incubation overnight at 4°C in PBS containing 2.5% dried milk and 0.5% Tween-20 and then incubated with a Ras-specific monoclonal antibody, Y13-259 (Furth, M.E., et al., (1982), Monoclonal antibodies to the p21 products of the transforming gene of Harvey murine sarcome virus and of the cellular ras gene family, **J. Virol. 43: 294-304**), in PBS containing 1% fetal calf serum for one hour at room temperature. After washing, membranes were incubated for one hour at room temperature with a 1:5000 dilution of secondary antibody, rabbit anti-rat IgG conjugated to horseradish peroxidase, in PBS containing 1% fetal calf serum. The presence of processed and unprocessed Ras-CVLS or Ras-CVLL was detected using a colorimetric peroxidase reagent (4-chloro-1-naphthol) as described by the manufacturer (Bio-Rad).

3. Cell Mat Assay:

Normal human HEPM fibroblasts were planted in 3.5 cm dishes at a density of 5 x 10^4 cells/dish in 2 ml growth medium, and incubated for 3-5d to achieve confluence. Medium was aspirated from each dish and the indicator tumor cells, T24-BAG4 human bladder carcinoma cells expressing an activated H-ras gene, were planted on top of the fibroblast

monolayer at a density of 2 x 10^3cells/dish in 2 ml growth medium, and allowed to attach overnight. Compound-induced colony inhibition was assayed by addition of serial dilutions of compound directly to the growth medium 24 h after tumor cell planting, and incubating cells for an additional 14 d to allow colony formation. Assays were terminated by rinsing monolayers twice with phosphate-buffered saline (PBS), fixing the monolayers with a 1% glutaraldehyde solution in PBS, then visualizing tumor cells by staining with X-Gal (Price, J., et al., Lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer, Proc. Natl. Acad. Sci.84, 156-160(1987)). In the colony inhibition assay, compounds were evaluated on the basis of two IC_{50} values: the concentration of drug required to prevent the increase in tumor cell number by 50% (tIC_{50}) and the concentration of drug required to reduce the density of cells comprising the cell mat by 50% (mIC_{50}). Both IC_{50} values were obtained by determining the density of tumor cells and mat cells by visual inspection and enumeration of cells per colony and the number of colonies under the microscope. The therapeutic index of the compound was quantitatively expressed as the ratio of mIC_{50}/tIC_{50}, with values greater than one indicative of tumor target specificity.

Additional assays were carried out by following essentially the same procedure as described above, but with substitution of alternative indicator tumor cell lines in place of the T24-BAG cells. The assays were conducted using either DLD-1-BAG human colon carcinoma cells expressing as activated K-ras gene or SW620-BAG human colon carcinoma cells expressing an activated K-ras gene. Using other tumor cell lines known in the art, the activity of the compounds of this invention against other types of cancer cells (such as those listed herein on pages 15 and 16) can be demonstrated.

4. Soft Agar Assay:

Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells are suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution is overlayed onto growth medium solidified with 0.6% agarose

containing the same concentration of farnesyl transferase inhibitor as the top layer. After the top layer is solidified, plates are incubated for 10-16 days at 37°C under 5% CO_2 to allow colony outgrowth. After incubation, the colonies are stained by overlaying the agar with a solution of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies are counted and the IC_{50}'s determined.

TABLE 1 - FPT INHIBITION

EXAMPLE	FPT IC_{50} (μM)	EXAMPLE	FPT IC_{50} (μM)
1	<0.034	2	0.010 0.016
4	0.046	16A	0.032 0.026
16B	0.038 0.023	11B	>0.095
15	0.022	7	0.012
8	0.021	11A	0.0018 0.0021
5	0.0023	12B	0.0025
9	0.0013	10	0.0019
7B	<0.003	8B	0.013
14A	0.0026	14	0.062
13A	0.078	13	0.005
5A	>0.099	7A	>0.1
8A	>0.094	10A	>0.094
9A	>0.088	6	0.0031
11	0.002	5B	~0.003
12A	>0.094	13B	0.005
14B	0.005	5 • HCl salt	0.0038
14A • HCl salt	<0.0031	9B	0.003
10B	0.003	17	0.043
17A	0.048	18	0.0031
19	<0.0038	20	0.0062
21	0.0084		

TABLE 2

COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

EXAMPLE	ENZYME INHIBITION FPT IC_{50} μM	ENZYME INHIBITION GGPT IC_{50} μM
2	0.010 0.016	>300
4	0.046	>35.7
5B	~0.003	>300
16A	0.032 0.026	>38
16B	0.038 0.023	>76
7	0.012	>300
11A	0.0018 0.0021	>66
9	0.0013	>59
5	0.0023	>66
14A	0.0026	>62
13	0.005	>63
7B	<0.003	>66
8B	0.013	>60
18	0.0031	>50
20	0.0062	>38

TABLE 3
ACTIVITY IN COS CELLS

Example	Inhibition of Ras Processing IC_{50} (μM)	Example	Inhibition of Ras Processing IC_{50} (μM)
8	<0.25	2	0.25
15	0.60	16A	0.5
16B	0.125	11	<0.25
7	<0.25	5B	0.05
10	<0.025	10A	2.0
12B	<0.025	12A	0.95
11A	<0.025	11B	2.25
5	0.098	14A • HCl salt	0.015
13	0.420	9	0.010
7B	0.025	8B	0.280
9A	0.85	5 • HCl salt	0.010
5A	5.0 1.0	14A	0.480
14	>1.0	13A	>1.0
7A	>1.0	8A	>1.0
17	0.350	17A	0.500
14B	0.045	6	0.040
18	0.025	19	0.045
20	~0.030	21	0.42

TABLE 4

INHIBITION OF TUMOR CELL GROWTH - MAT ASSAY

Example	Tumor (T-24) IC_{50} (μM)	Tumor (DLD-1) IC_{50} (μM)	Tumor (SW620) IC_{50} (μM)	Normal IC_{50} (μM)
1	< 1.6	--	--	>25
4	3.1	--	--	>25
7	<1.6	<1.6	6.25	>25
5B	<1.6	3.1	10	>25
13B	<1.6	3.1	>3.1	25
11B	<1.6	8	18	>25
9A	<1.6	12.5	12.5	18
10A	<1.6	2.0	1.6	8
5	<1.6	3.1	6.25	>25
14A	<1.6	6.25	12.5	>25
13A	3.1	6.25	6.25	>25
7B	<1.6	1.6	3.1	>25
8A	<1.6	<1.6	3.1	>25
2	<1.6	6.25	6.25	>25
16B	<1.6	6.25	25	>25
8	<1.6	3.1	3.1	>25
15	3.1	6.25	>6.25	>25
11A	<1.6	<1.6	>6.25	>25
9	<1.6	<1.6	6.25	>25
10	<1.6	<1.6	3.1	>25
12A	<1.6	2.0	4	>25
5A	12.5	12.5	>25	>25
14	<1.6	6.25	>12.5	>25
13	<1.6	3.1	>1.6	>25
8B	<1.6	<1.6	3.1	>25
17	1.6	6.25	25	>25
17A	3.1	4	18	>25
10B	<1.6	1.6	1.6	>25
12B	<1.6	3.1	6.25	>25
7A	<1.6	1.6	3.1	>25
6	<1.6	4.0	6.24	--
19	<1.6	<1.6	6.25	>25

INHIBITION OF HUMAN TUMOR CELL GROWTH - SOFT AGAR ASSAY

A Soft Agar Assay was done with the compound of Example 10 and the following tumor cell lines: K ras NIH 3T3; H ras NIH 3T3; HTB 177 (NSCLC) K ras mutation; HTB 173 (NCI H146) (SCLC) ras mut. not detected; A549 (lung) K ras mutation; HTB 175 (SCLC) ras mut. not detected; HTB 119 (NCI H69) (SCLC); HTB 183 (NCI H661) (NSCLC) ras mut. not detected; HPAF II (pancreatic) K ras mutation; MCF-7 (breast) ras mut. not detected; HBL100 (breast) ras mut. not detected; Du4475 (breast) ras mut. not detected; MDA MB 468 (breast) ras mut. not detected; DU 145 (prostate) ras mut. not detected; MDA MB453 (breast); BT474 (breast); PC3 (prostate); DLD 1 (colon) K ras mutation; and AsPc-1 (pancreatic) K ras mutation. Ras mutation status determined by ELISA (Oncogene Science). The IC_{50} (μM) for each cell line was within the range of 0.04 and 3.0.

A Soft Agar Assay was done with the compound of Example 18 and the following tumor cell lines: K ras NIH 3T3; H ras NIH 3T3; HTB 177 (NSCLC) K ras mutation; A549 (lung) K ras mutation; and HTB 175 (SCLC) ras mut. not detected. Ras mutation status determined by ELISA (Oncogene Science). The IC_{50} (μM) for each cell line was within the range of 0.175 and 0.8.

RESULTS:

1. Enzymology:

The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as very potent (IC_{50} <<0.1 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. This selectivity is important for the therapeutic potential of the compounds used in the methods of this invention, and increases the potential that the compounds will

have selective growth inhibitory properties against Ras-transformed cells.

2. Cell-Based: COS Cell Assay

Western blot analysis of the Ras protein expressed in Ras-transfected COS cells following treatment with the tricyclic farnesyl protein transferase inhibitors of this invention indicated that they inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras (see Table 3). The compound of Example 2, for example, inhibited Ras-CVLS processing with an IC_{50} value of 0.025 μM, but did not block the geranylgeranylation of Ras-CVLL at concentrations up to 33 μM.

These results provide evidence for specific inhibition of farnesyl protein transferase, but not geranylgeranyl transferase I, by compounds of this invention in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

3. Cell-Based: Cell Mat Assay

Tricyclic farnesyl protein transferase inhibitors of this invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay without displaying cytotoxic activity against the normal monolayer.

In Vivo Anti-Tumor Studies:

Tumor cells (5×10^5 to 8×10^6) of DLD-1 (human colon carcinoma cells, ATCC # CCL 221) are innolculated subcutaneously into the flank of 5-6 week o;d athymic nu/nu female mice. Tumor bearing animals are selected and randomized when the tumors are established. Animals are treated with vehicle (β-cyclodextrin for i.p. or corn oil for p.o.) only or with a compound of the present invention in vehicle four times a day (QID) for 7 days per week for 4 weeks. The percent inhibition of tumor growth relative to vehicle controls is determined by tumor measurements.

The average % tumor inhibition for each compound of Examples 1, 2, 4, 5, 6, 7, 7A, 8B, 9, 10, 11A, 11B, 12B, 13, 14A,

16B, and 18 was 7 to 50% for a dose of 10 mg/kg p.o, and 35.4 to 83 for a dose of 50 mg/kg p.o.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A
Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B
Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

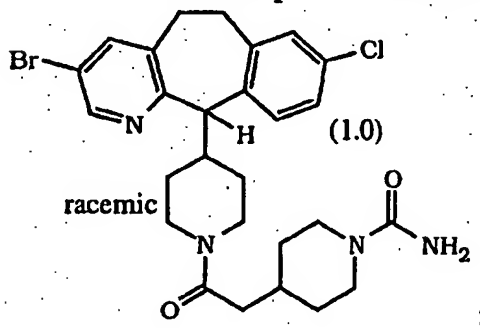
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of:



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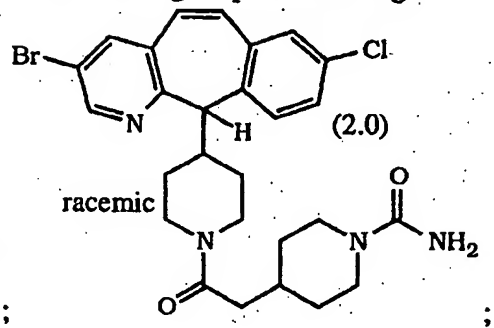

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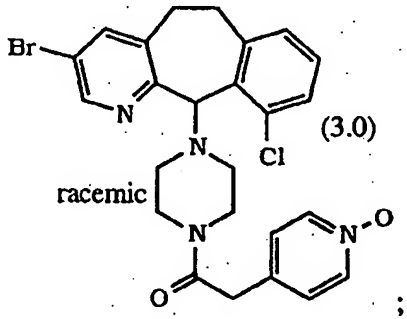

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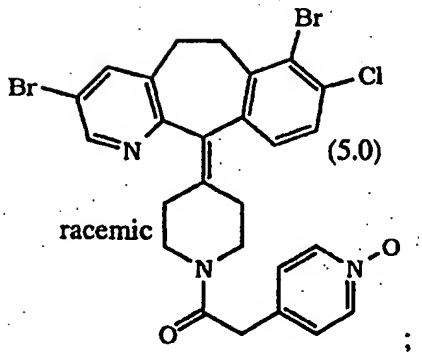

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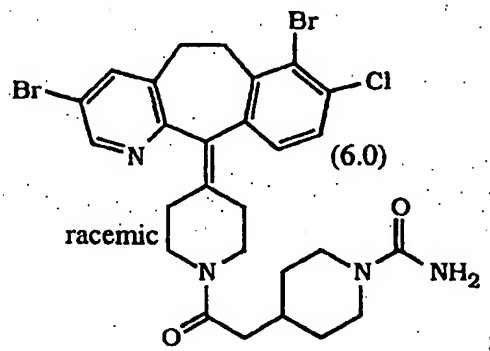

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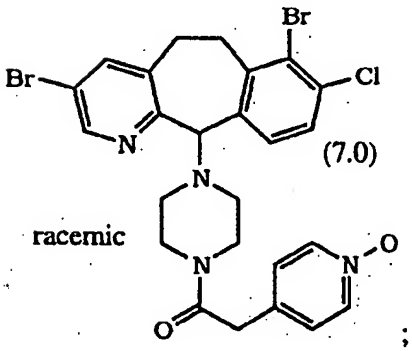

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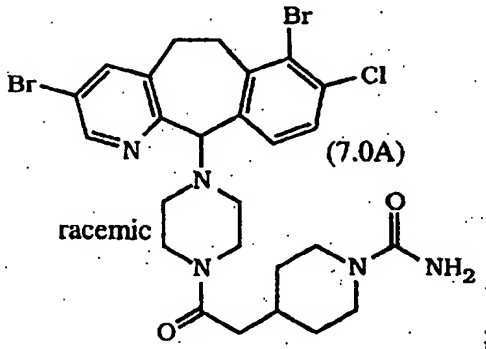

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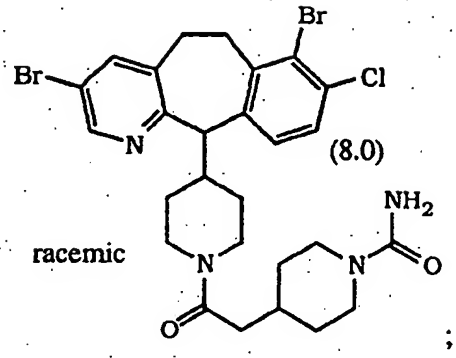
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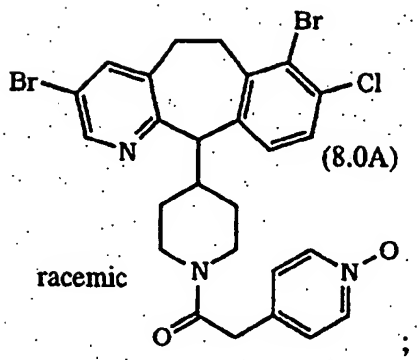
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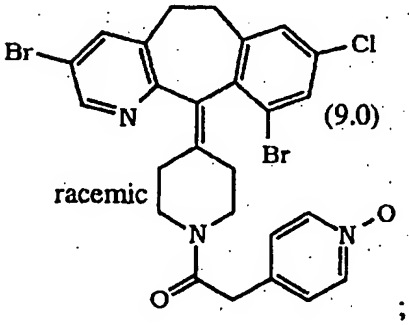
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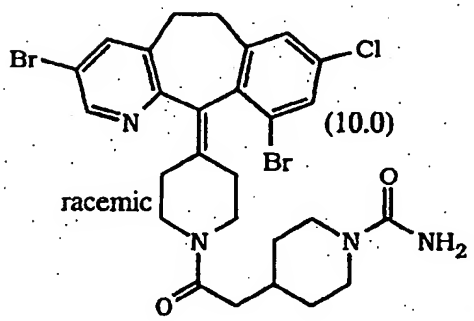
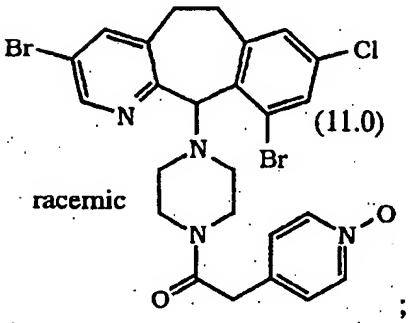
N
O
O

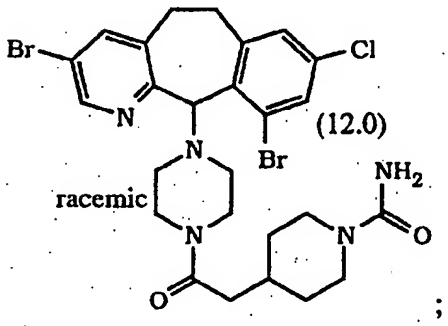
;


Br
Cl
N
(10.0)
Br
racemic
O
N
NH2
O

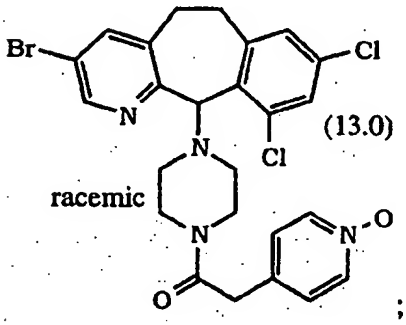
;


Br
Cl
N
(11.0)
Br
racemic
N
N
O
O

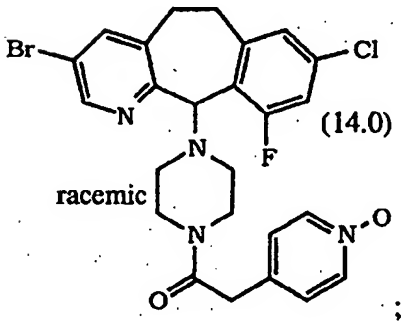
;


Br
Cl
N
(12.0)
Br
racemic
NH2
N
N
O
O

;


Br
Cl
N
(13.0)
Cl
racemic
N
N
O
O

;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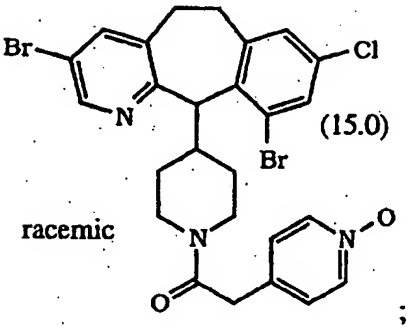
Cl
N
(14.0)
F
racemic
N
N
O
O

;



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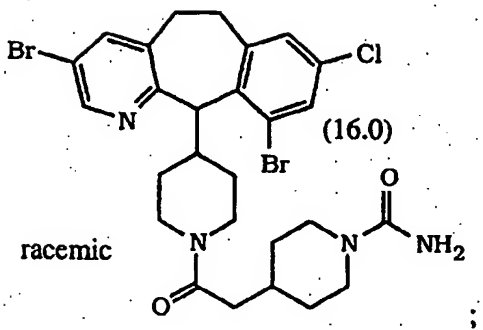

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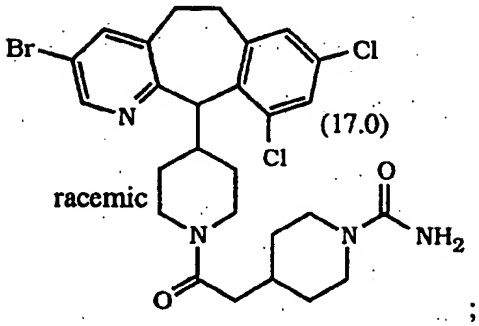

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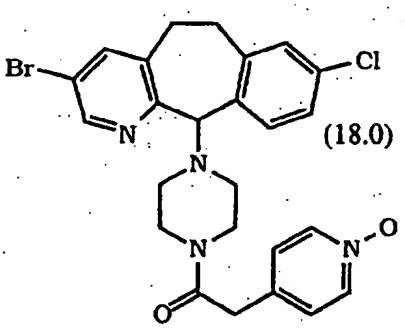

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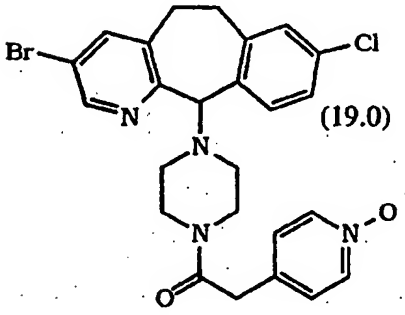

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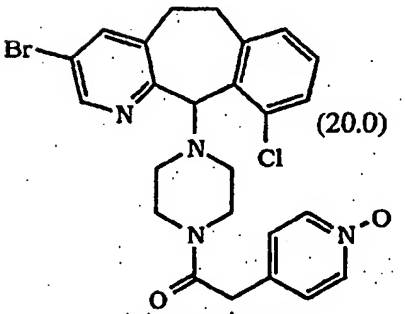
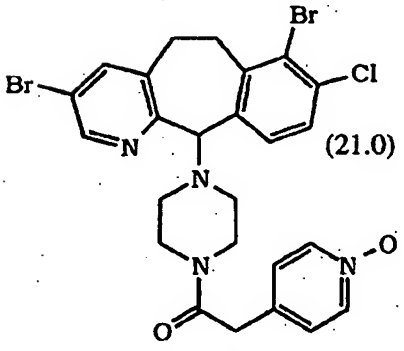


(+)-enantiomer ;



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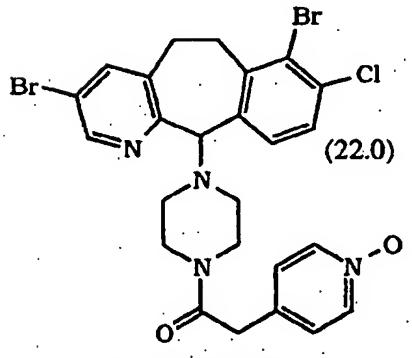

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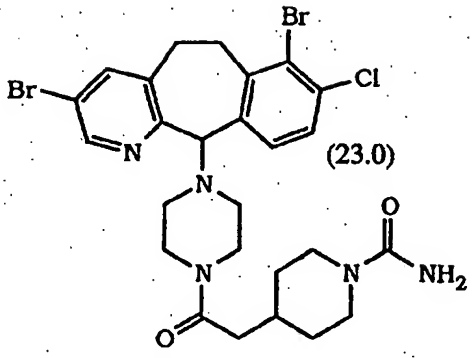
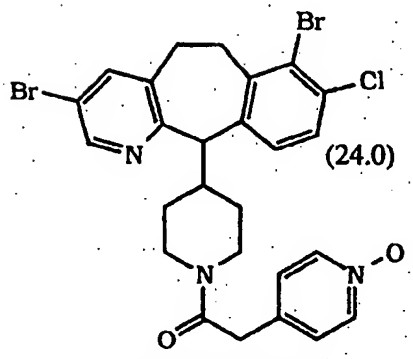


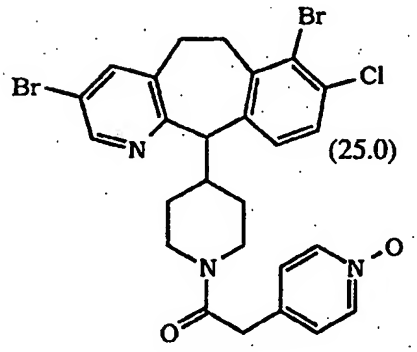
(23.0)

(-) - enantiomer ;



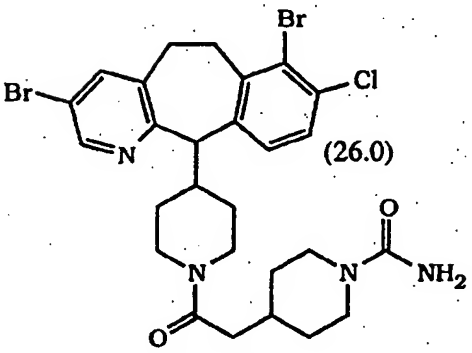
(24.0)

(+) - enantiomer ;



(25.0)

(-) - enantiomer ;



(26.0)

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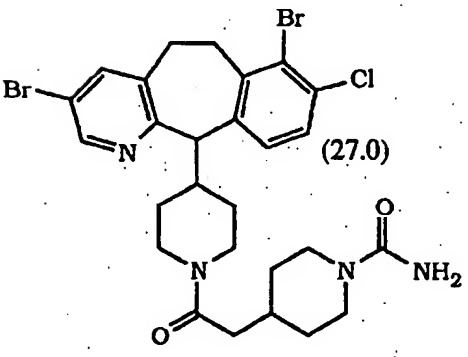
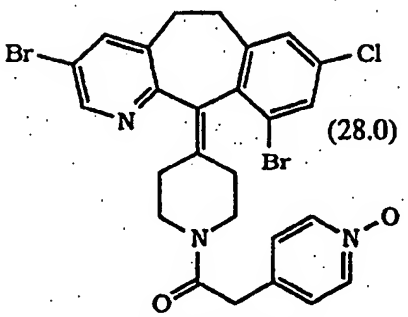


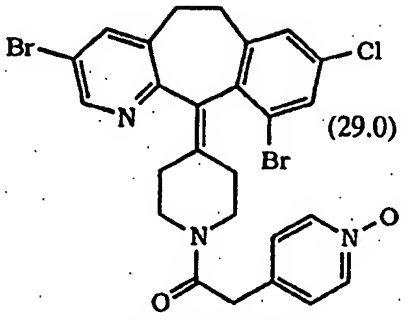
(27.0)

(-) - enantiomer ;

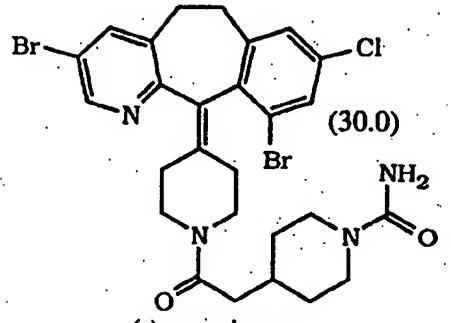


(28.0)

(-)-enantiomer ;


(29.0)

(+)-enantiomer ;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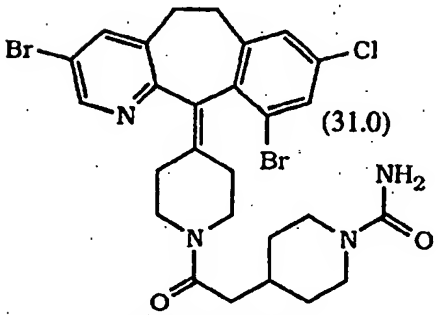
(31.0)

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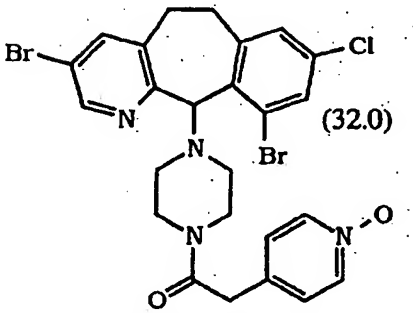
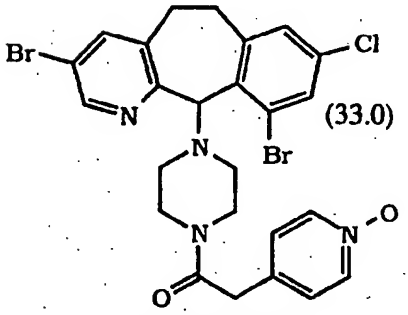
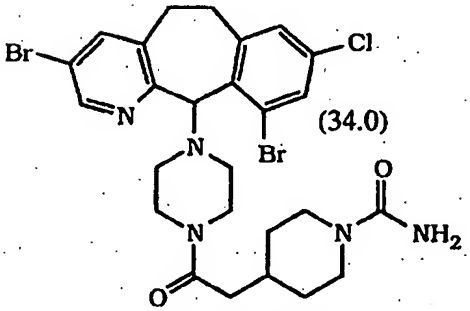

(32.0)

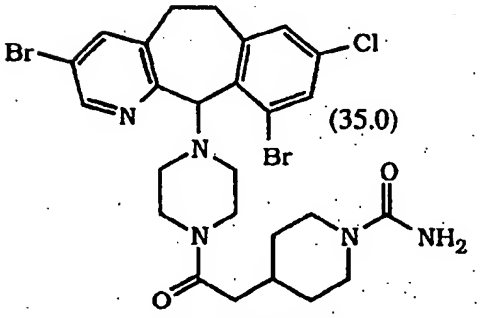
(+) - enantiomer ;


(33.0)

(-) - enantiomer ;


(34.0)

(+) - enantiomer ;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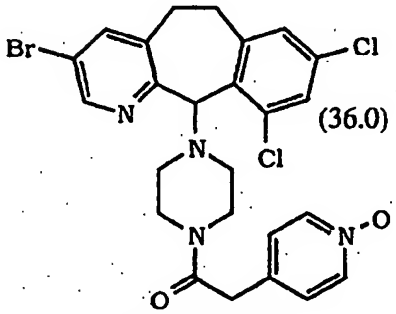
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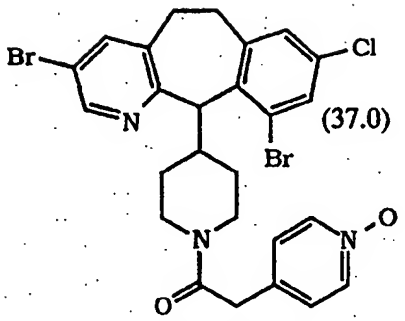

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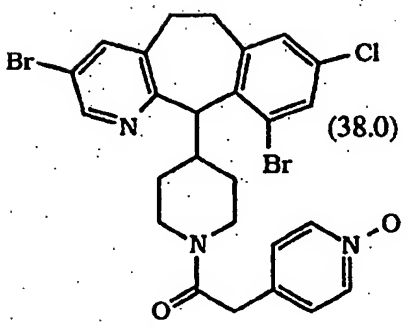

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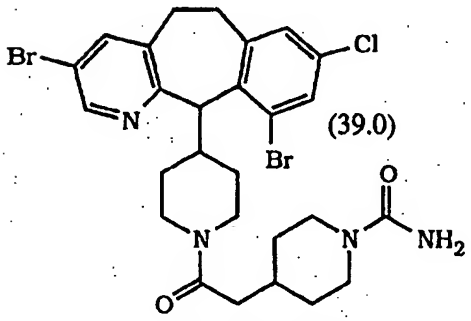

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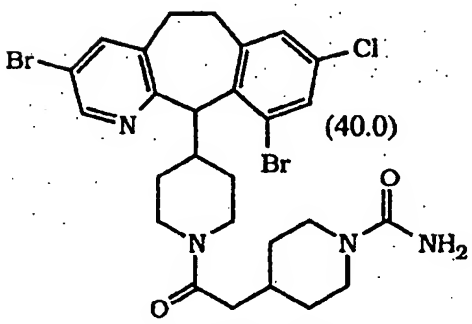

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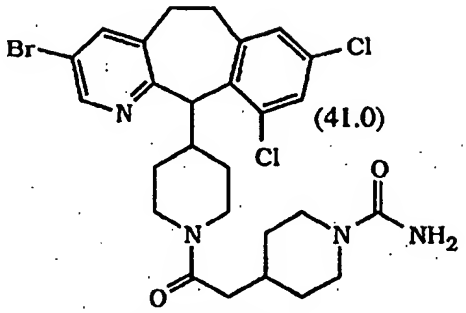

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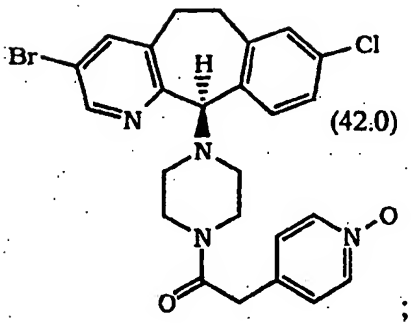

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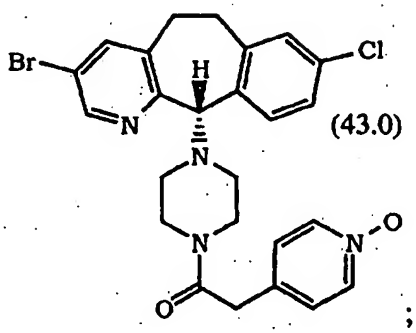

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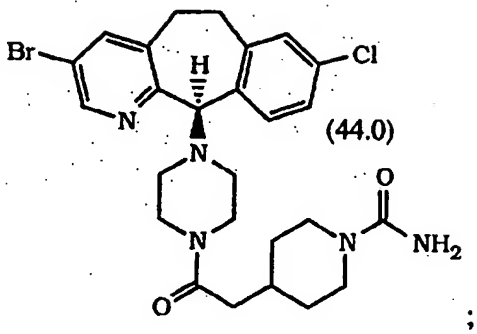
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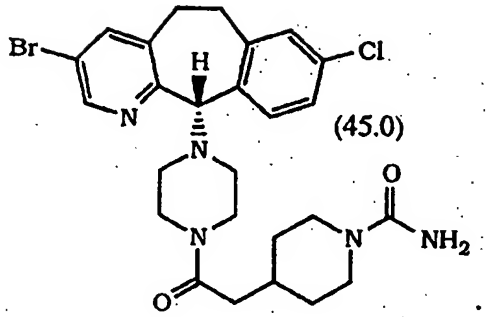
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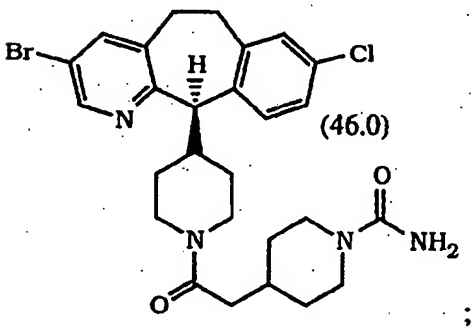
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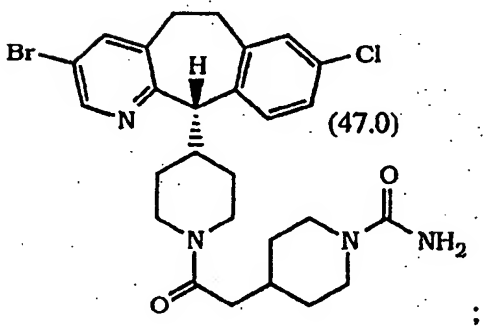
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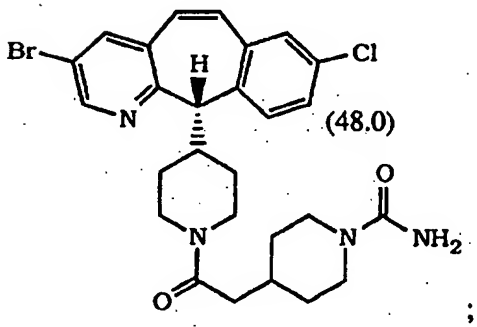
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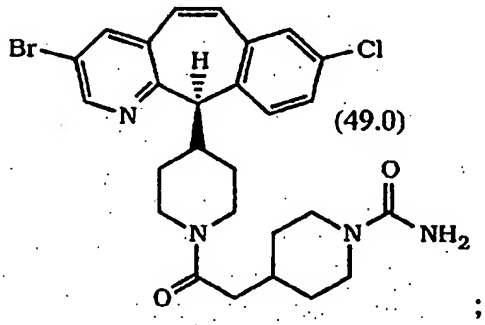
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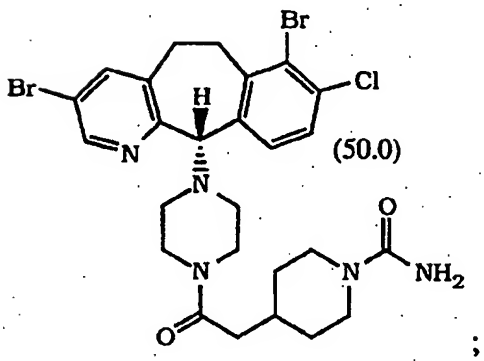
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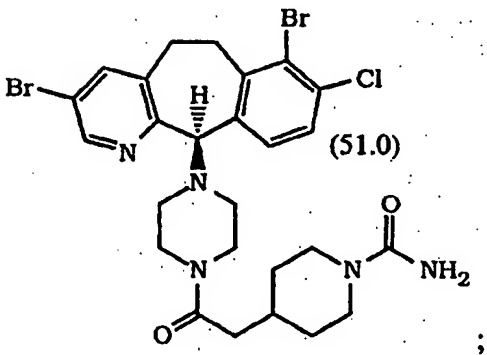
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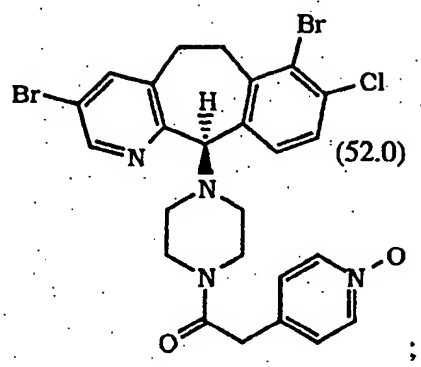
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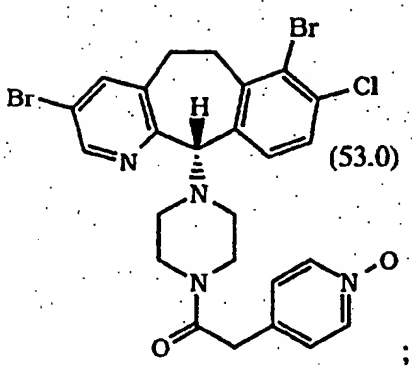
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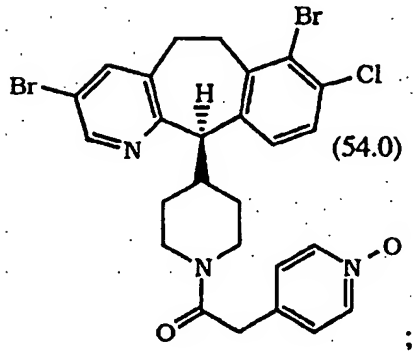
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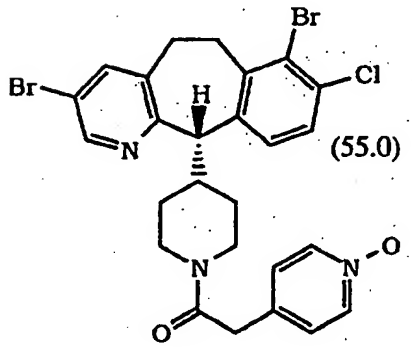
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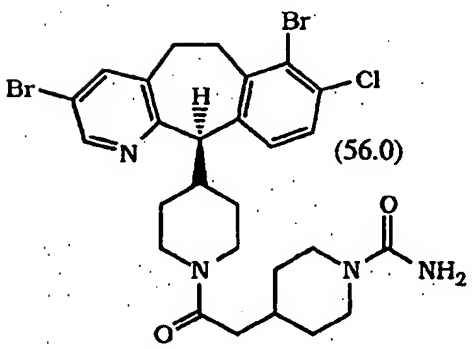
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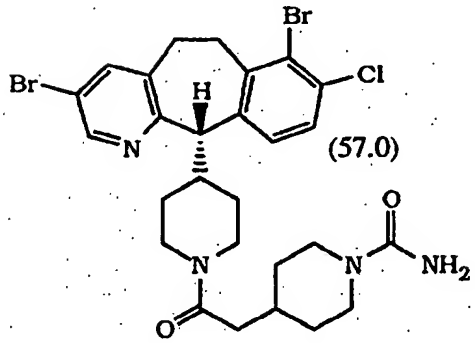
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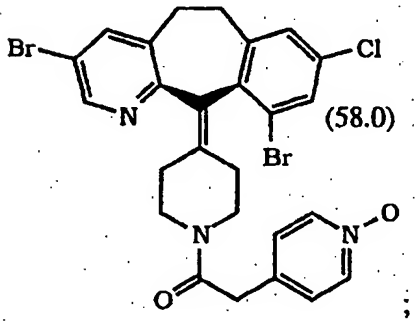
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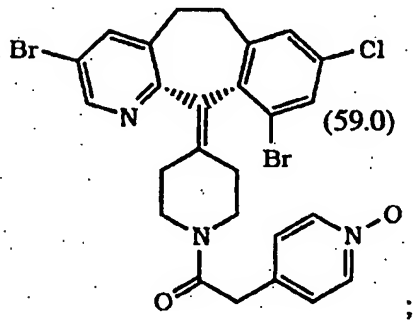
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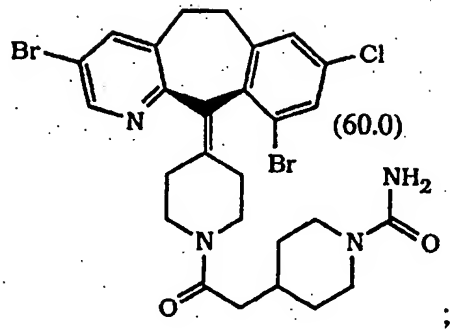
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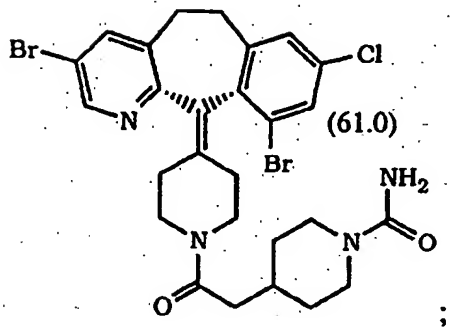
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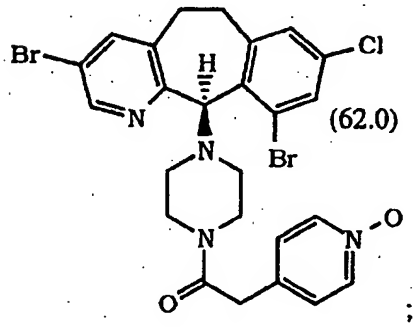
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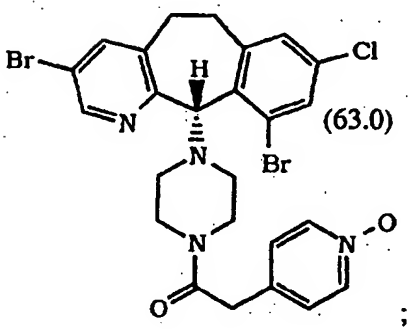
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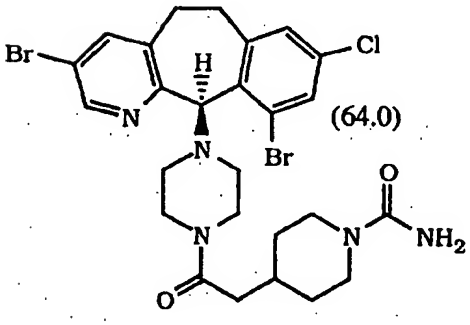
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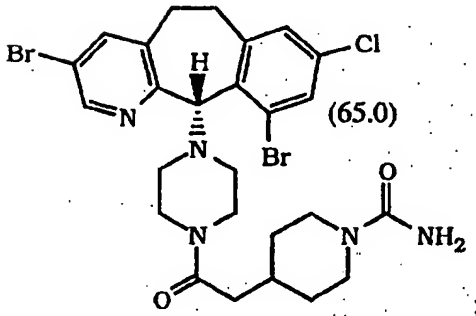
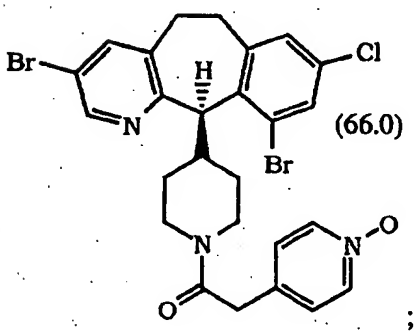
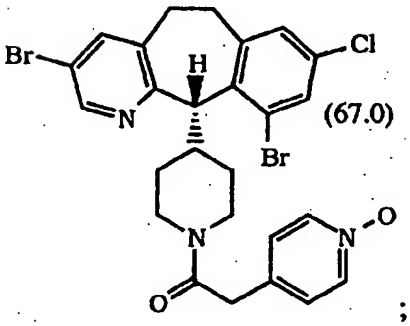

(65.0)

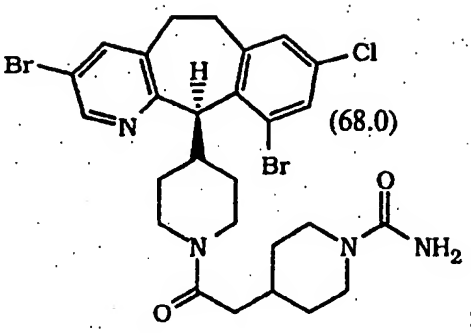
;

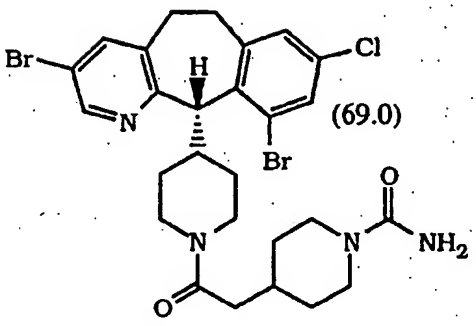

(66.0)

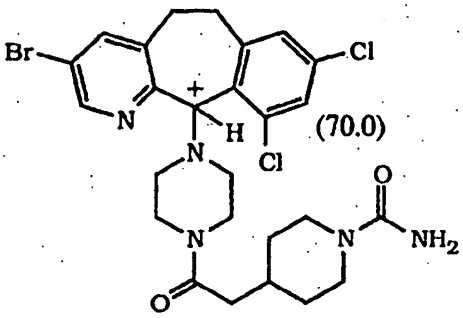
;

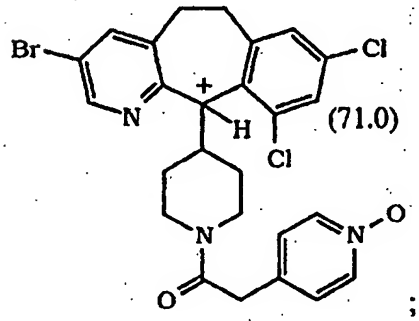

(67.0)

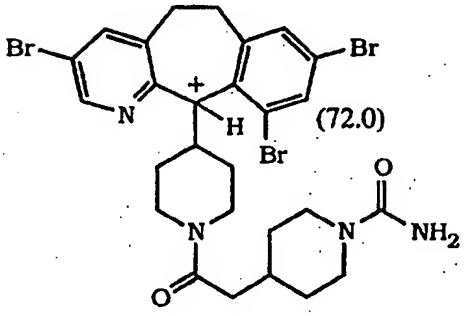
;

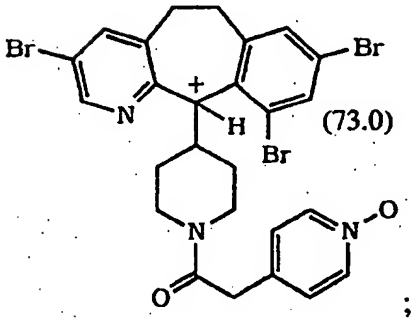

(68.0) ;

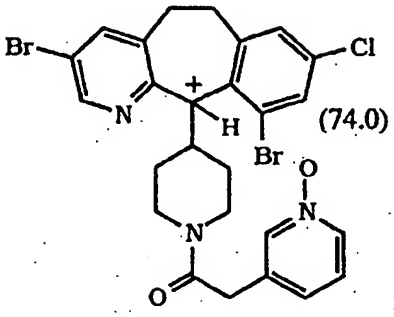

(69.0) ;

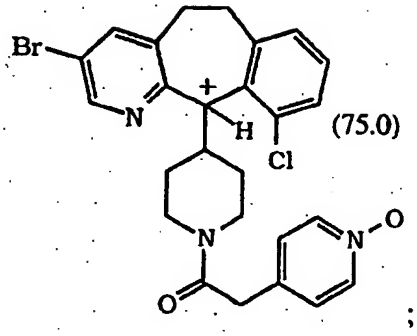

(70.0) ;


(71.0) ;

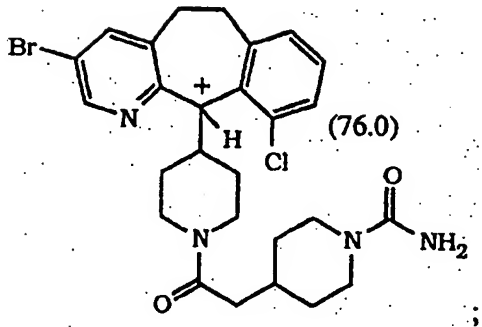

(72.0) ;


(73.0) ;

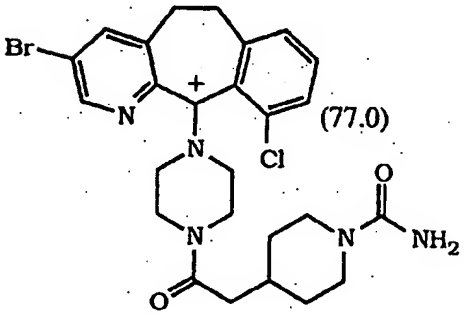

(74.0) ;


(75.0)

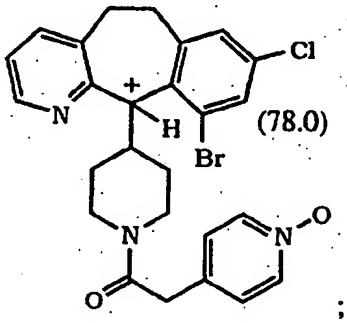
;


(76.0)

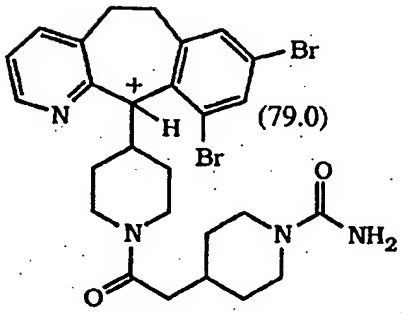
;

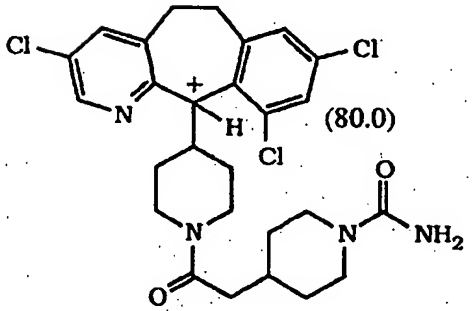

(77.0)

;


(78.0)

;

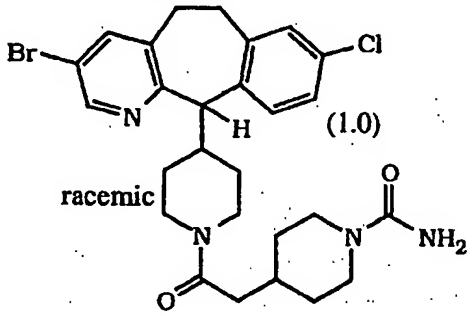

(79.0)


(80.0)

; and

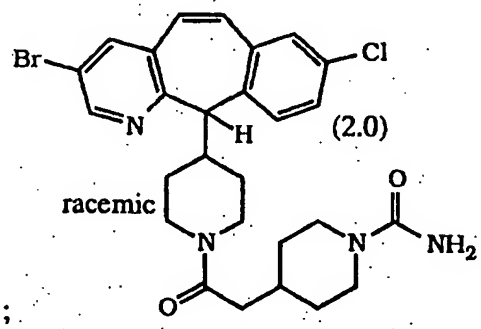
or pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 selected from the group consisting of:


(1.0)

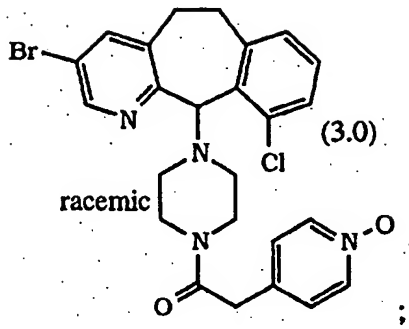
racemic

;

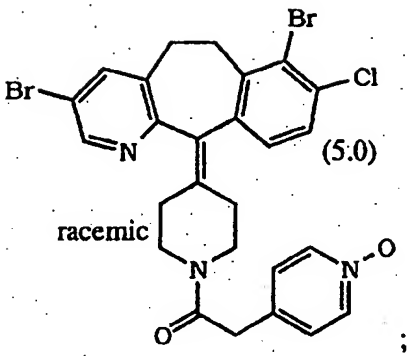

(2.0)

racemic

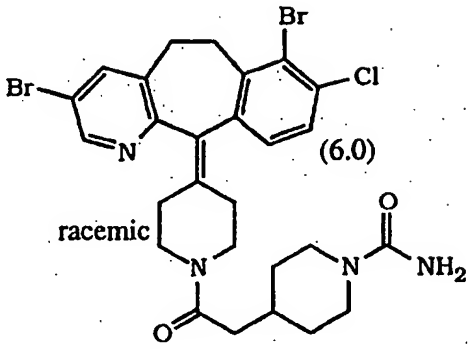
;


Br
N
Cl
(3.0)
racemic
N
N
O
O

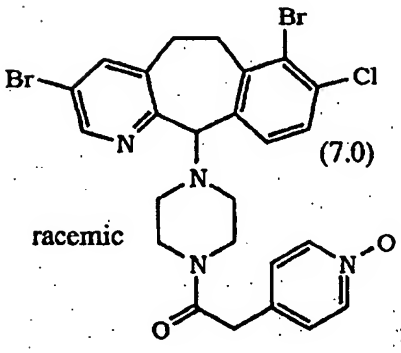
;


Br
Br
N
Cl
(5.0)
racemic
N
N
O
O

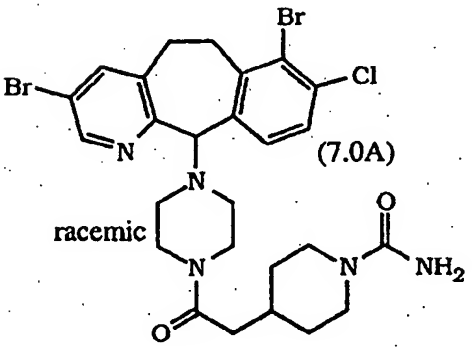
;


Br
Br
N
Cl
(6.0)
racemic
N
O
N
NH2
O

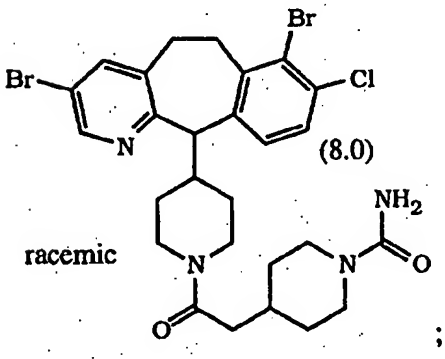
;


Br
Br
N
Cl
(7.0)
racemic
N
N
O
O

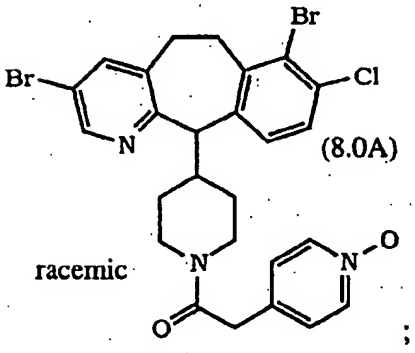
;


Br
Br
N
Cl
(7.0A)
racemic
N
O
N
NH2
O

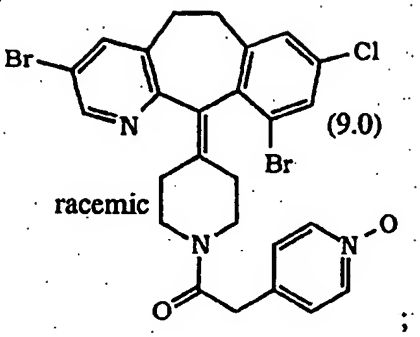
;


Br
Br
N
Cl
(8.0)
racemic
NH2
N
O
O

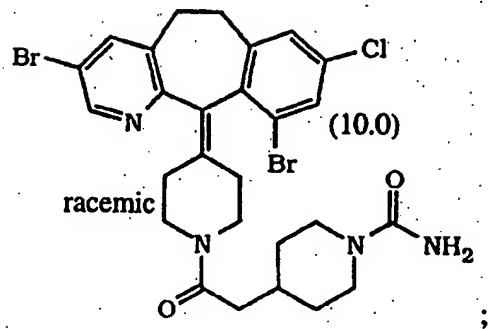
;


Br
Br
N
Cl
(8.0A)
racemic
N
N
O
O

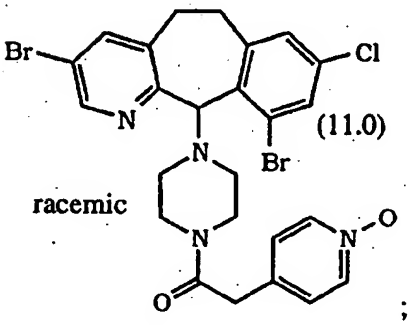
;


Br
Cl
N
(9.0)
Br
racemic
N
N-O
O

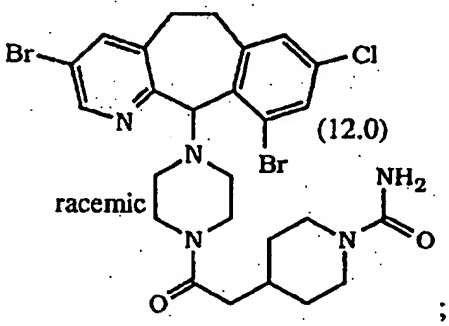
;


Br
Cl
N
(10.0)
Br
racemic
O
N
NH2
O

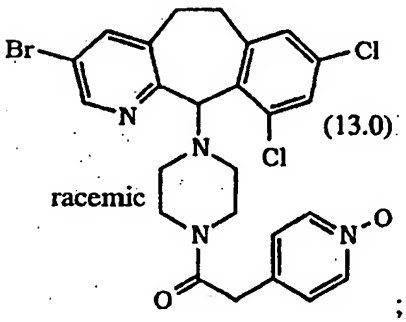
;


Br
Cl
N
(11.0)
N
Br
racemic
N
N-O
O

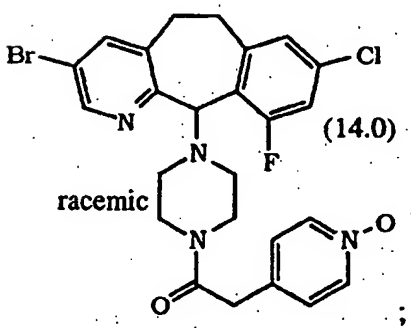
;


Br
Cl
N
(12.0)
N
Br
NH2
racemic
N
O
O

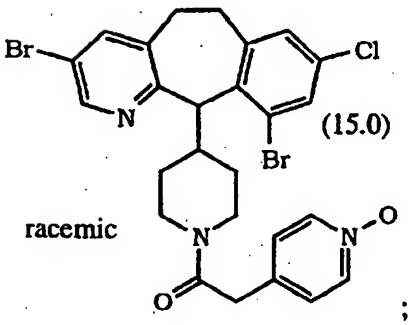
;


Br
Cl
N
(13.0)
N
Cl
racemic
N
N-O
O

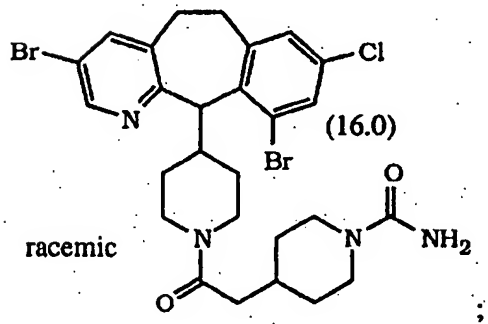
;


Br
Cl
N
(14.0)
N
F
racemic
N
N-O
O

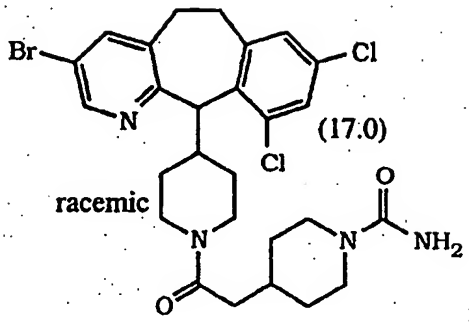
;


Br
Cl
N
(15.0)
Br
racemic
N
N-O
O

;

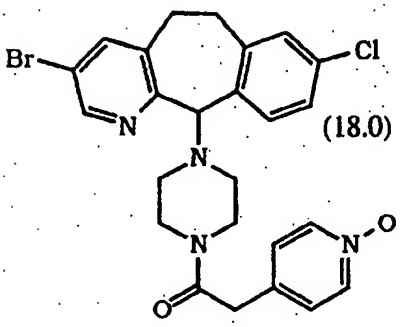

Br
Cl
N
(16.0)
Br
racemic
O
N
NH2
O

;



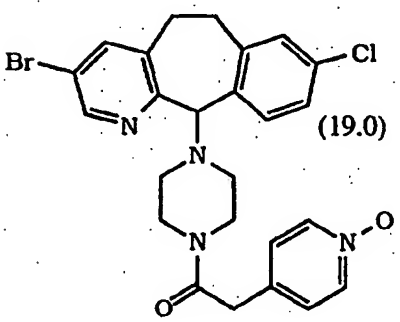
(17.0)

;



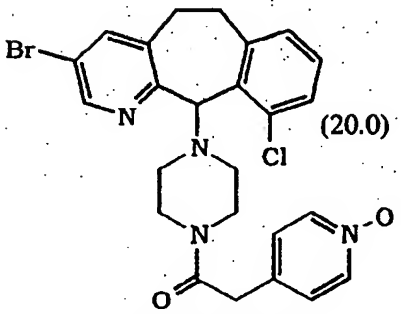
(18.0)

(+) - enantiomer ;



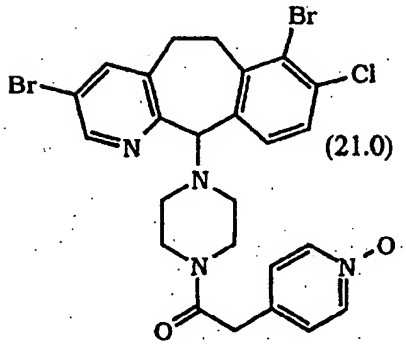
(19.0)

(-) - enantiomer ;



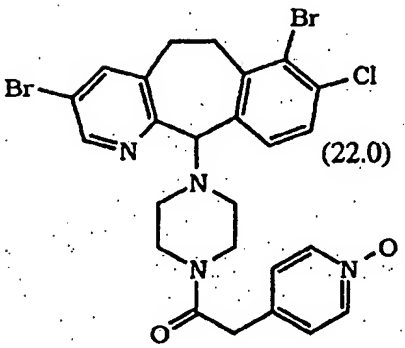
(20.0)

(+)-enantiomer ;



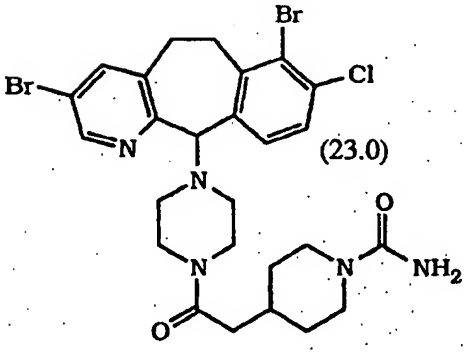
(21.0)

(+) - enantiomer ;



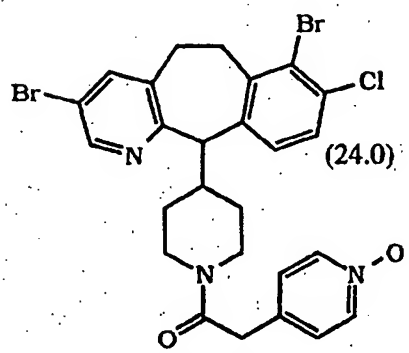
(22.0)

(-) - enantiomer ;



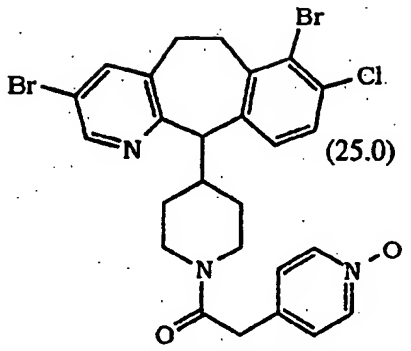
(23.0)

(-) - enantiomer ;

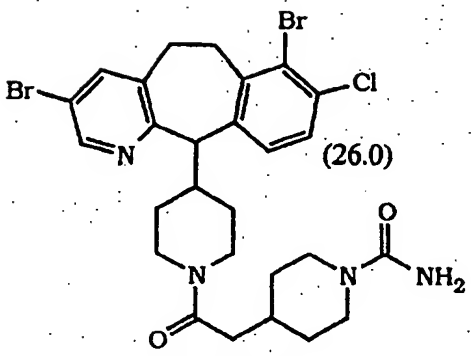


(24.0)

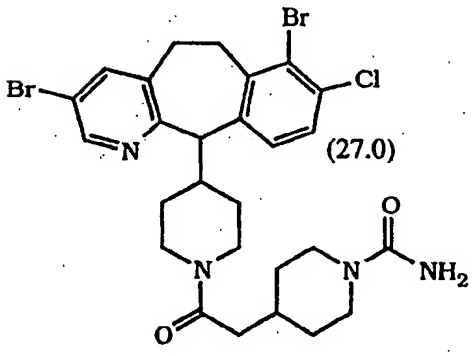
(+) - enantiomer ;



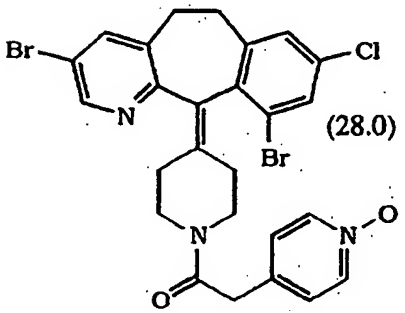
(-) - enantiomer ;



(+) - enantiomer ;

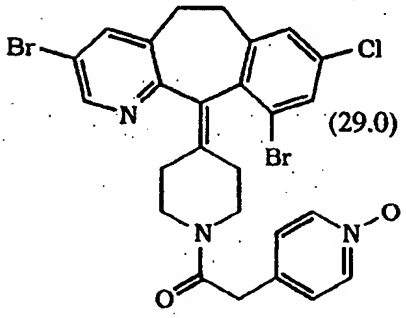


(-) - enantiomer ;

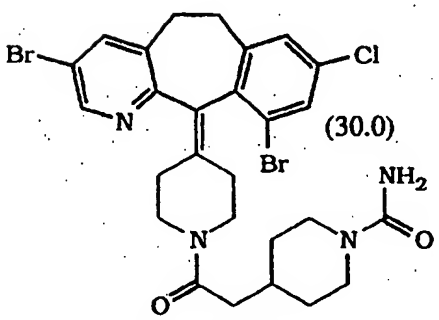


(-)-enantiomer ;

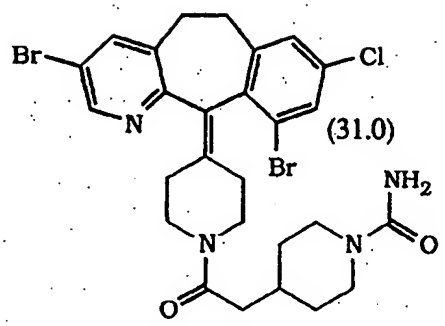
5



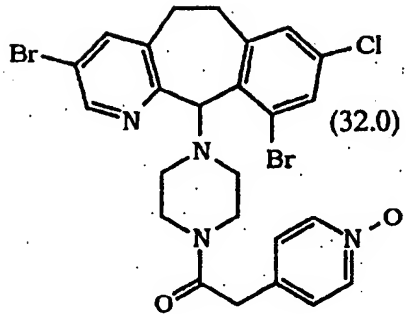
(+)-enantiomer ;



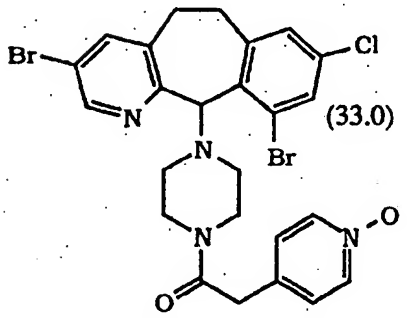
(-)-enantiomer ;


(31.0)

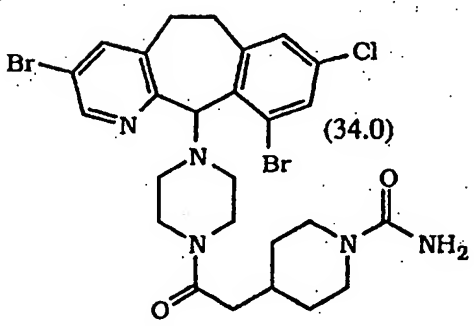
(+)-enantiomer ;


(32.0)

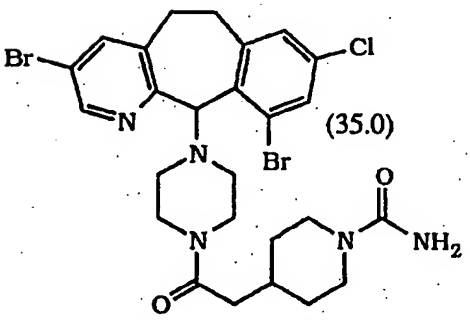
(+) - enantiomer ;


(33.0)

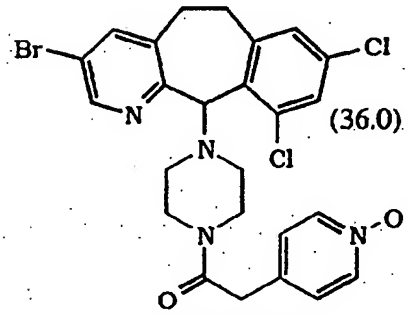
(-) - enantiomer ;


(34.0)

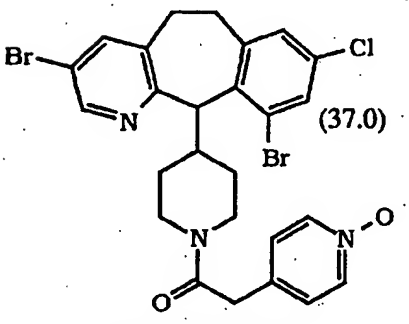
(+) - enantiomer ;


(35.0)

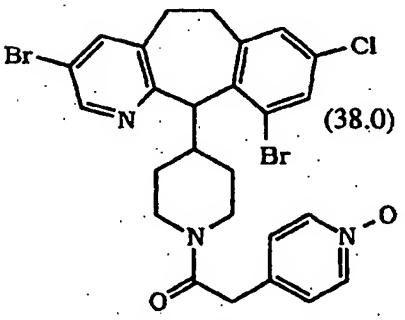
(-) - enantiomer ;


(36.0)

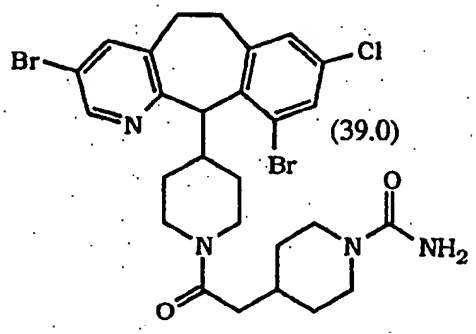
(+)-enantiomer ;


(37.0)

(+) - enantiomer ;

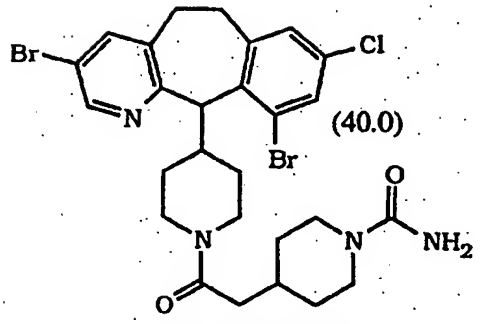

(38.0)

(-) - enantiomer ;



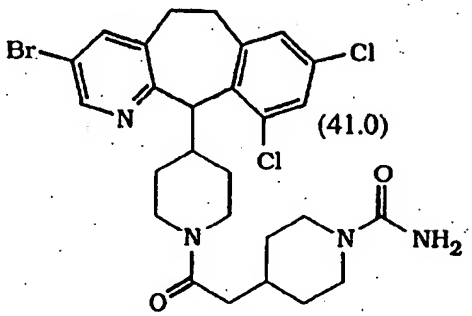
(39.0)

(+) - enantiomer ;



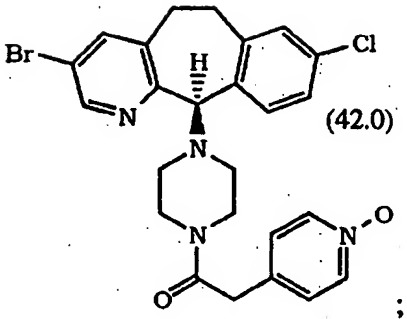
(40.0)

(-) - enantiomer ;



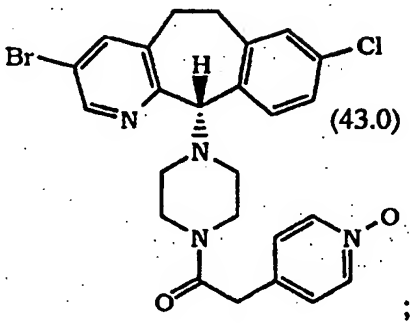
(41.0)

(+)-enantiomer ;



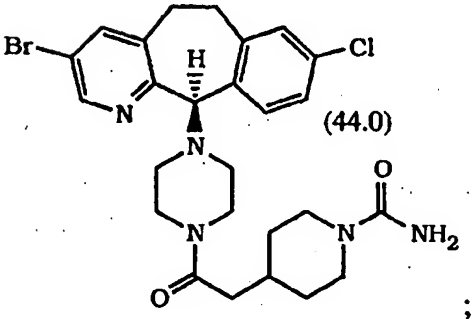
(42.0)

;



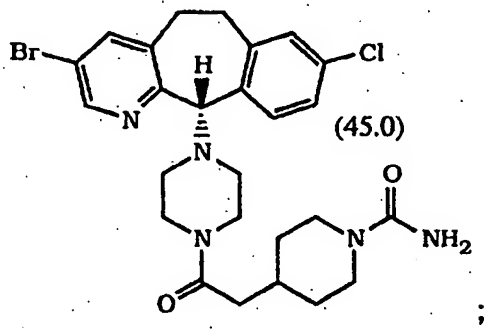
(43.0)

;



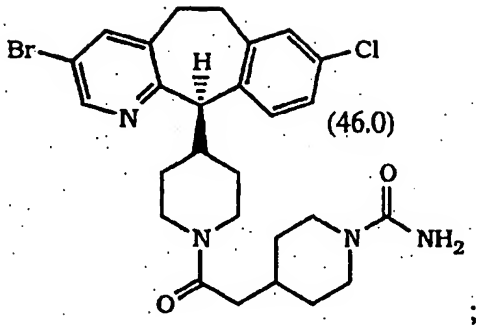
(44.0)

;

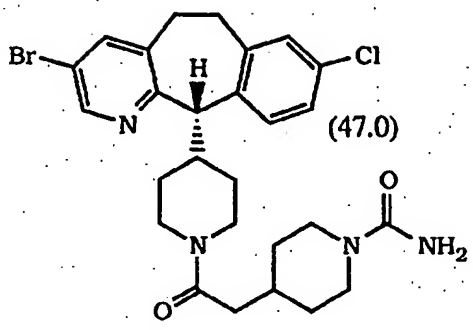


(45.0)

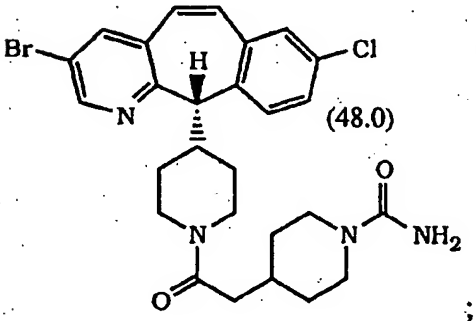
;


(46.0)

;


(47.0)

;


(48.0)

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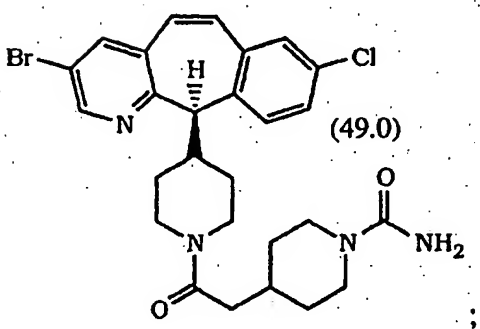
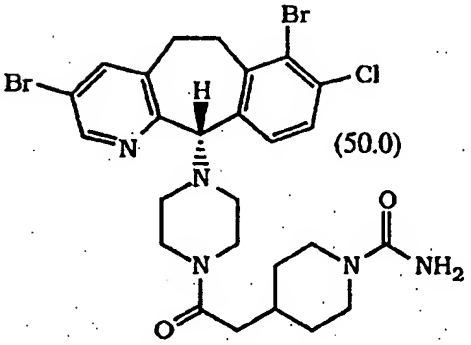
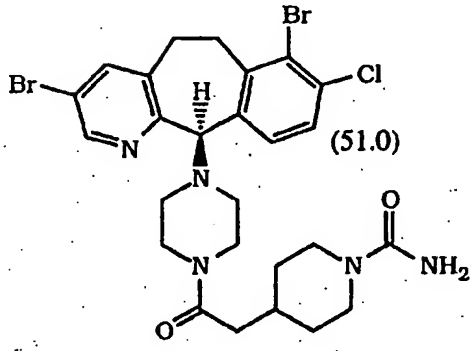

(49.0)

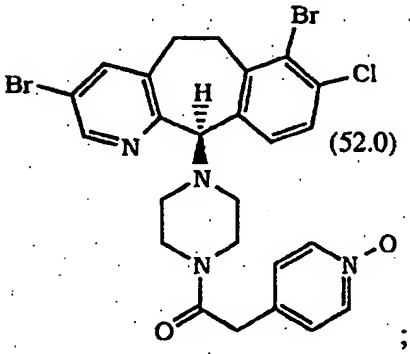
;


(50.0)

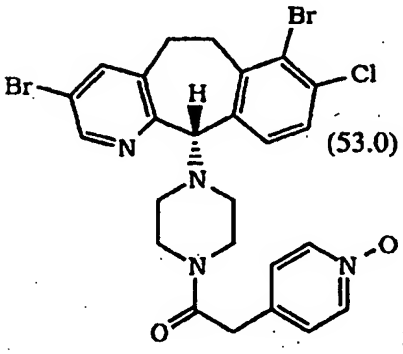
;


(51.0)

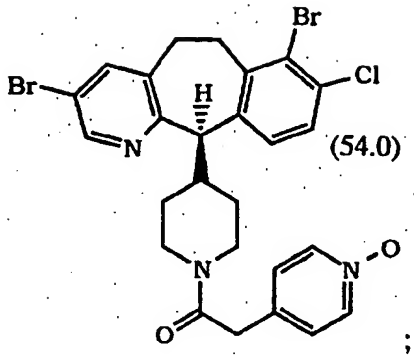
;

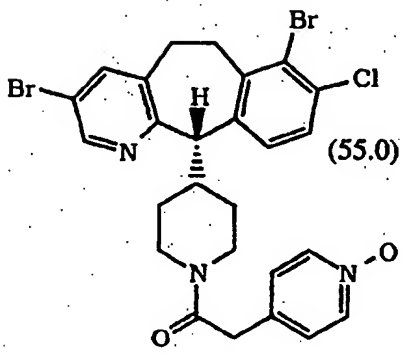

(52.0)

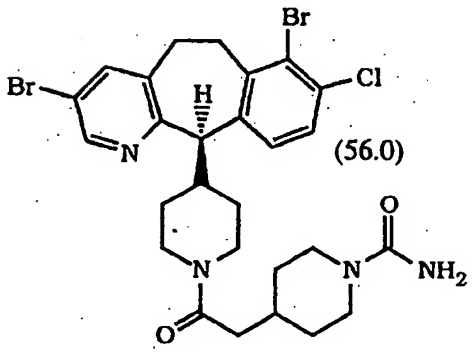
;

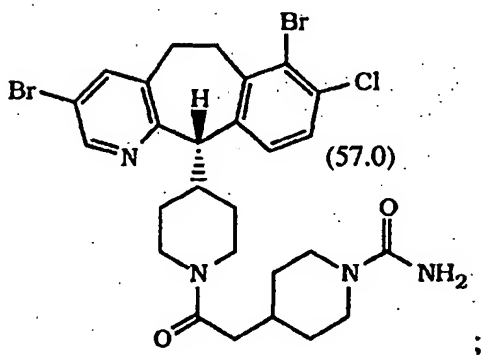

(53.0)

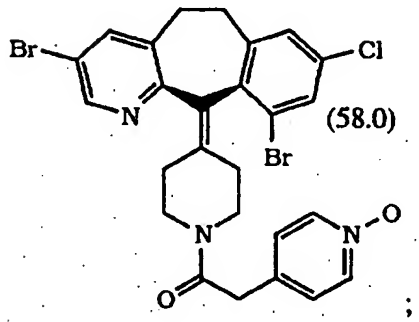
;

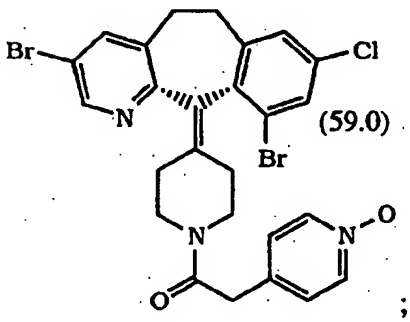

(54.0) ;

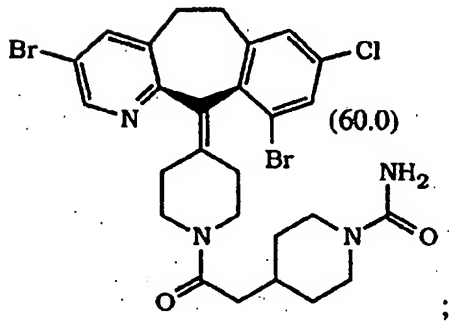

(55.0)

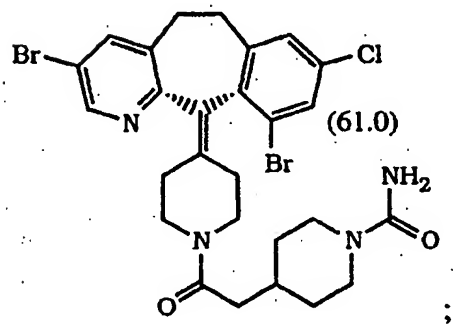

(56.0) ;

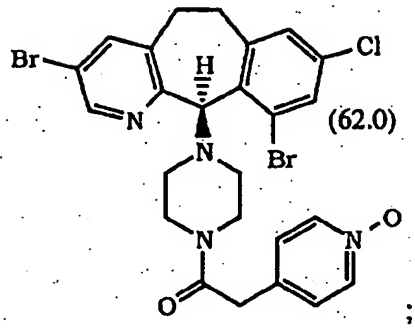

(57.0) ; ;


(58.0) ;


(59.0) ;


(60.0) ;


(61.0) ;


(62.0)

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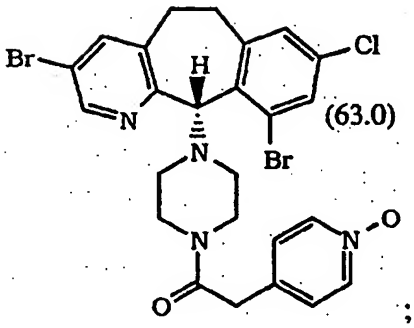
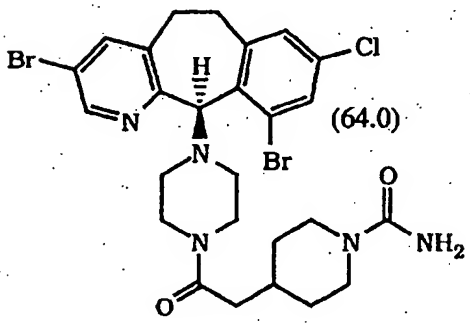

(63.0)

;


(64.0)

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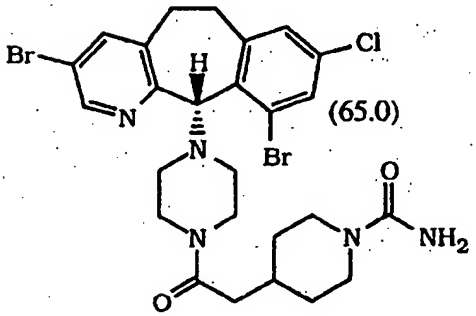
(65.0)

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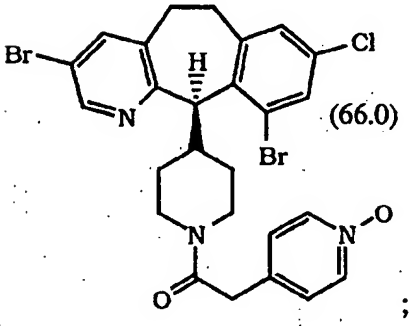
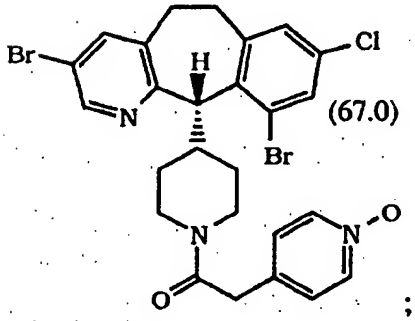

(66.0)

5 ;


(67.0)

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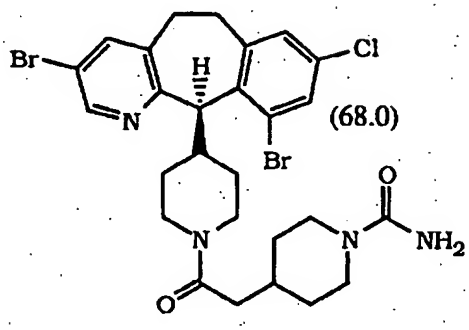
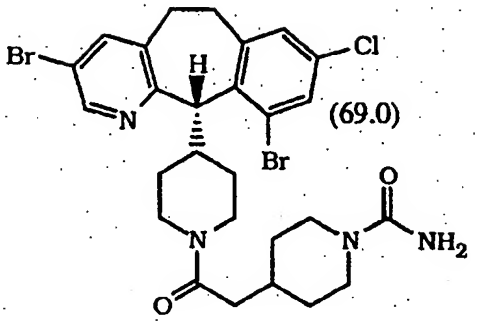
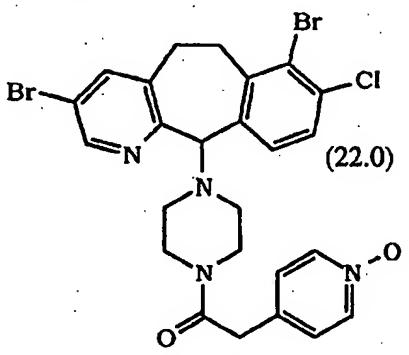

(68.0)

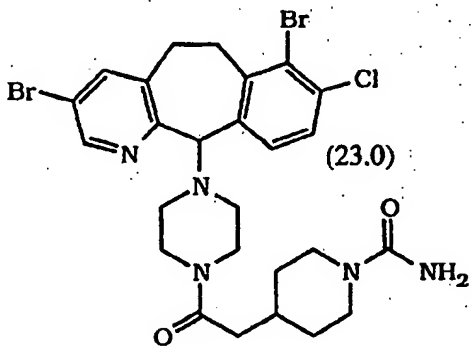
; and



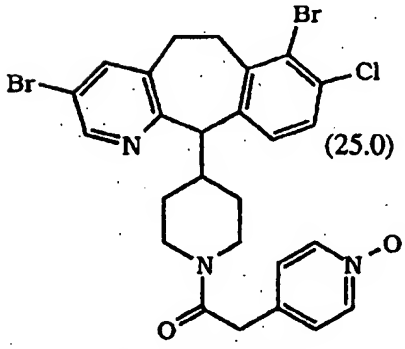
3. The compound of Claim 1 selected from the group consisting of:



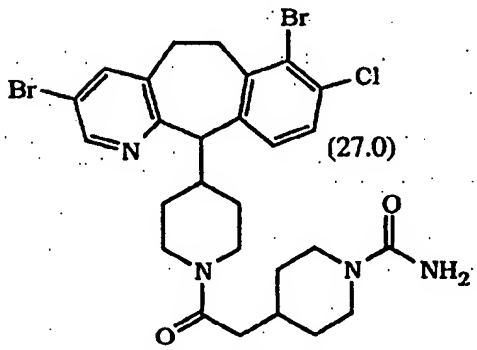
(-) - enantiomer ;



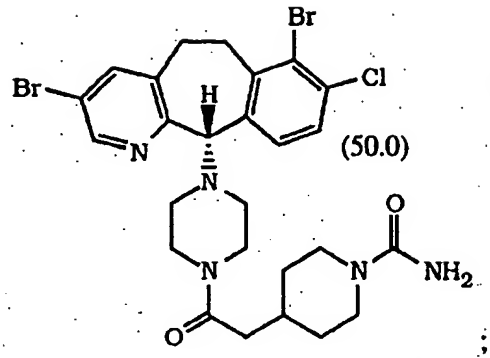
(-) - enantiomer ;

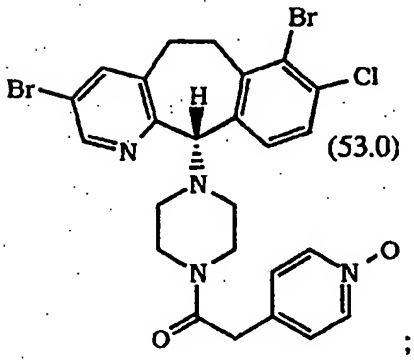


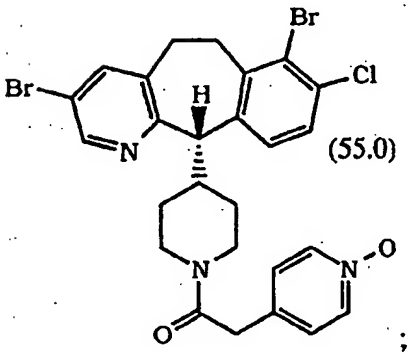
(-) - enantiomer ;

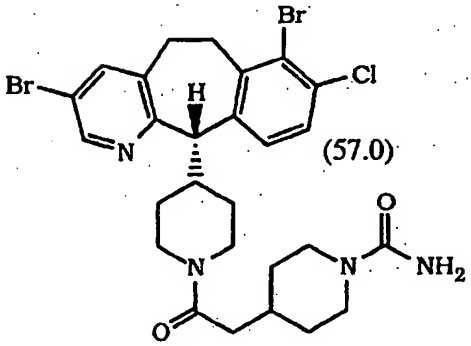


(-) - enantiomer ;

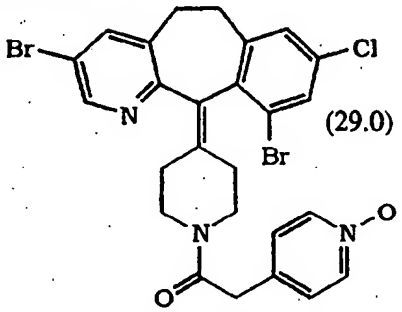

(50.0) ;

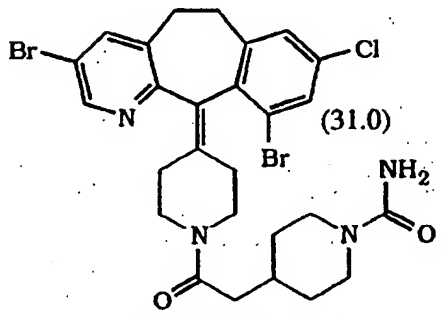

(53.0) ;

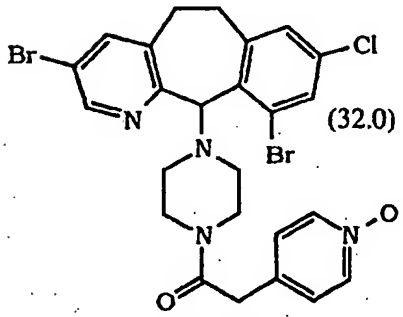

(55.0) ; and

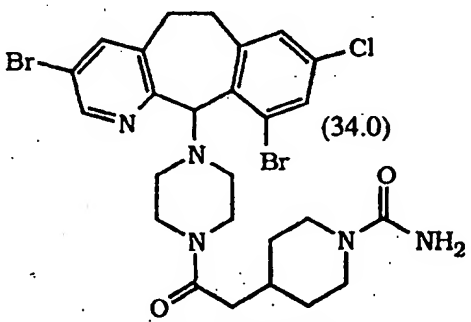

(57.0)

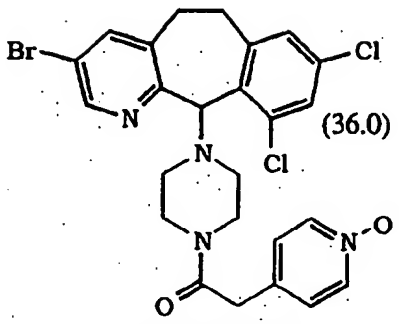
4. The compound of Claim 1 selected from the group consisting of:


(29.0)
(+)-enantiomer ;

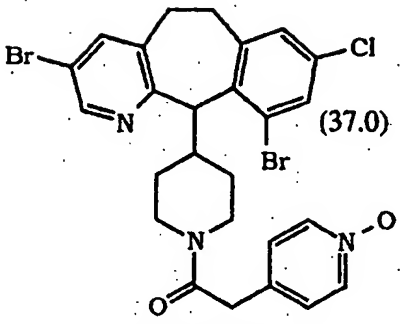

(31.0)
(+)-enantiomer ;


(32.0)
(+) - enantiomer ;

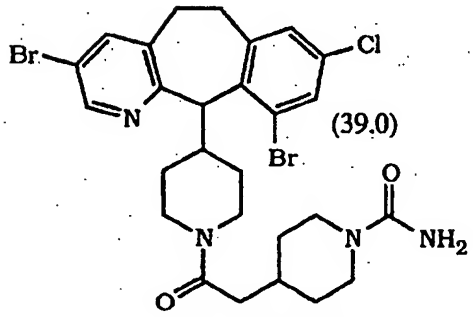

(34.0)
(+) - enantiomer ;



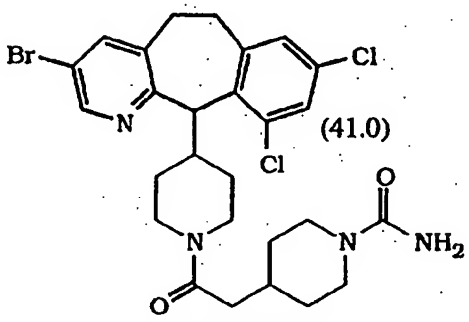
(+)-enantiomer ;



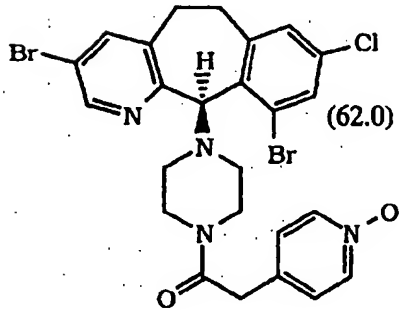
(+) - enantiomer ;



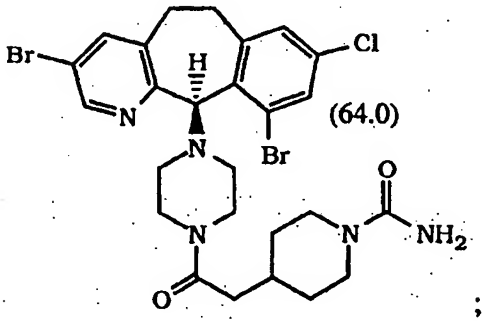
(+) - enantiomer ;



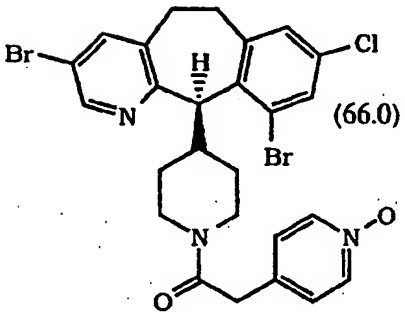
(+)-enantiomer ;



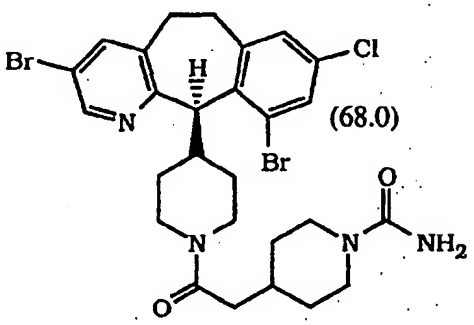
5 ;



;

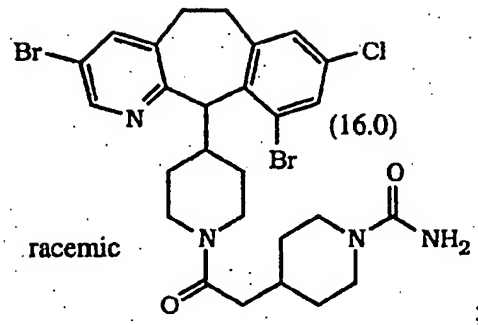


; and

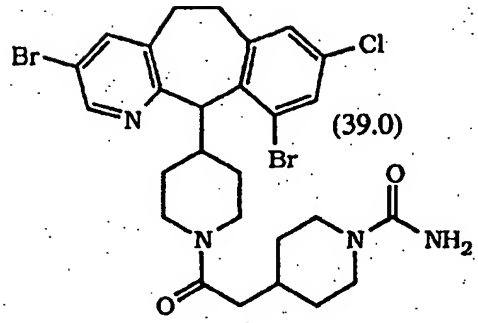


.

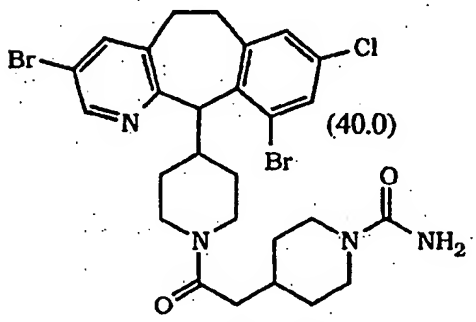
5. A compound selected from the group consisting of:



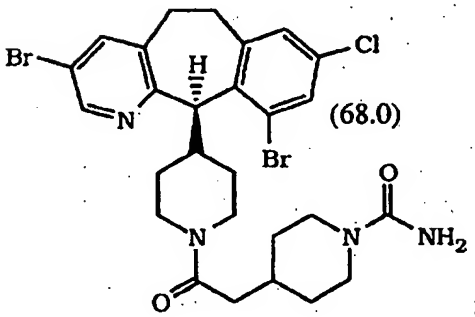
racemic ;



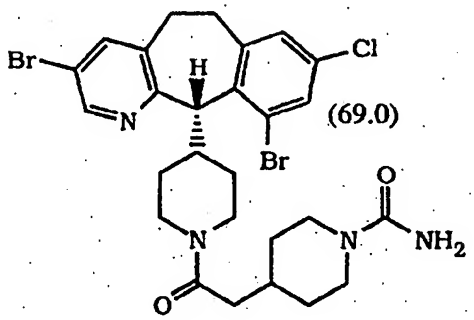
(+) - enantiomer ;



(-) - enantiomer ;

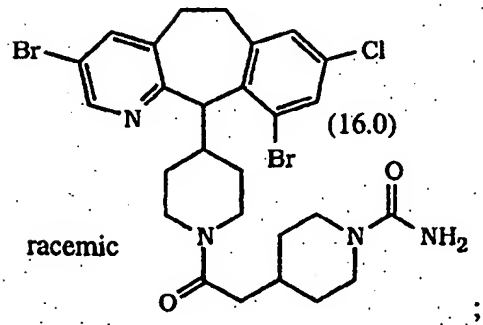


;

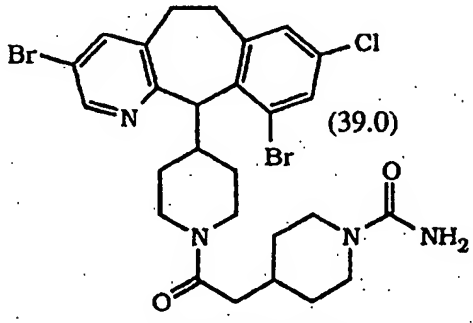


and .

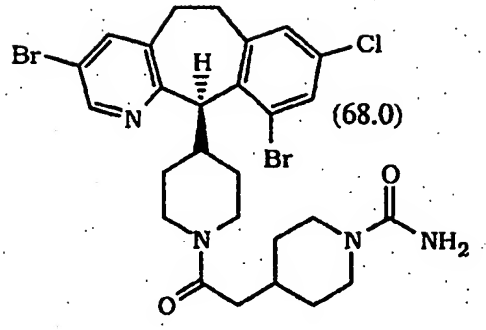
6. The compound of Claim 5 selected from the group consisting of:



racemic ;

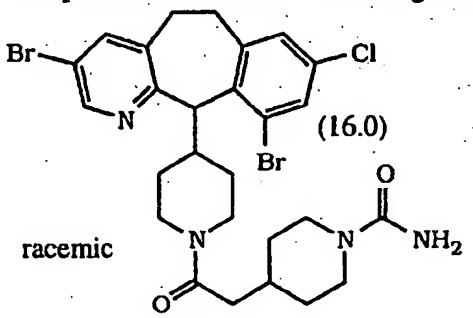


(+) - enantiomer ;



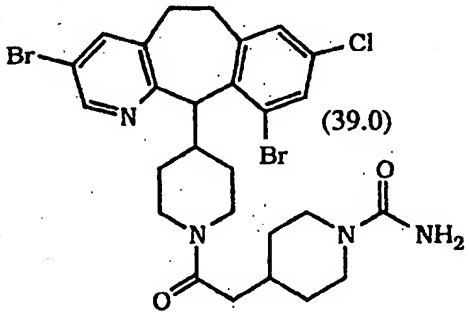
and

7. The compound of Claim 5 having the formula:



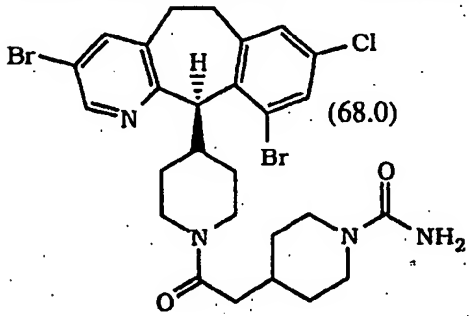
5

8. The compound of Claim 5 having the formula:



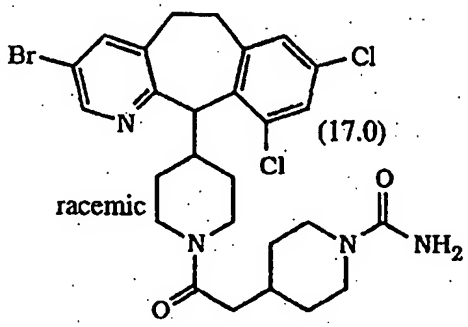
(+) - enantiomer

9. The compound of Claim 5 having the formula:

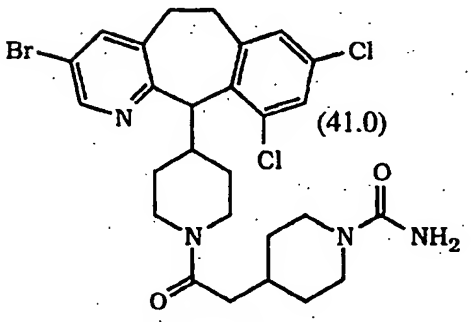


10

10. The compound of Claim 1 selected from the group consisting of:



and



(+)-isomer

11. A pharmaceutical composition comprising an effective amount of a compound of any of Claims 1 to 10 in combination with a pharmaceutically acceptable carrier.

12. The use of a compound of any of Claims 1 to 10 for the manufacture of a medicament for the inhibition of farnesyl protein transferase.

13. The use of a compound of any of Claims 1 to 10 for the manufacture of a medicament for the treatment of pancreatic cancer, lung cancer, myeloid leukemia, thyroid follicular cancer, myelodysplastic syndrome, epidermal carcinoma, bladder carcinoma, colon cancer, breast cancer or prostate cancer.

14. The use of a compound of any of Claims 1 to 10 for for the inhibition of farnesyl protein transferase in a patient in

need of such treatment comprising administering an effective amount of a compound of any of Claims 1 to 10.

15. The use of a compound of any of Claims 1 to 10 for the treatment of pancreatic cancer, lung cancer, myeloid leukemia, thyroid follicular cancer, myelodysplastic syndrome, epidermal carcinoma, bladder carcinoma, colon cancer, breast cancer or prostate cancer in a patient in need of such treatment comprising administering an effective amount of a compound of any of Claims 1 to 10.

16. The use of a compound of any of Claims 1 to 10 for the manufacture of a medicament for inhibiting the abnormal growth of cells.

17. The use of a compound of any of Claims 1 to 10 for the manufacture of a medicament for inhibiting the abnormal growth of cells wherein the cells inhibited are tumor cells expressing an activated ras oncogene.

18. The use of a compound of any of Claims 1 to 10 for the manufacture of a medicament for inhibiting the abnormal growth of cells wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

19. The use of a compound of Claims 11 for the manufacture of a medicament for inhibiting farnesyl protein transferase.

20. The use of a compound of Claims 11 for the manufacture of a medicament for the treatment of pancreatic cancer, lung cancer, myeloid leukemia, thyroid follicular cancer, myelodysplastic syndrome, epidermal carcinoma, bladder carcinoma, colon cancer, breast cancer or prostate cancer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/19603

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 C07D401/14 C07D401/12 A61K31/44 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 10516 A (SCHERING CORP.) 20 April 1995 cited in the application see page 109, step C; pages 146-147, example 227; page 152, example 234; pages 185-186, example 351; page 212, examples 360 and 361; page 220, examples 351 and 354; page 2 line 23 to page 3, line 5; claims 1,13,21,28,29 ---	1-4, 11-13, 16-20
Y	WO 95 10515 A (SCHERING CORP.) 20 April 1995 see page 88, example 30; page 90, step C; claims 1,13,28-30; page 2, line 21 to page 3, line 3 --- -/--	1-4, 11-13, 16-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1997	21.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/19603

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 396 083 A (SCHERING CORP.) 7 November 1990 see claims 1,13,15; page 56, table 6, compound with R2 = Br ---	1-4,11
P,X	WO 96 30363 A (SCHERING CORP.) 3 October 1996 see claims; pages 27-31; page 62, examples 400-C and 400-F; page 95, example 425-H; page 114, example 502 ---	1-4, 11-13, 16-20
A,P	WO 96 30018 A (SCHERING CORP.) 3 October 1996 see claims ---	1-13, 16-20
A,P	WO 96 31478 A (SCHERING CORP.) 10 October 1996 see claims; page 15, group 122.0; page 93, example 32-A; page 101, step C; pages 102-104, examples 38-40 -----	1-13, 16-20

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/ 19603

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 14-15
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/19603

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9510516 A	20-04-95	AU 7970394 A	04-05-95
		CA 2174104 A	20-04-95
		EP 0723540 A	31-07-96
		JP 8510760 T	12-11-96
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		DE 69014393 T	01-06-95
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		IE 66392 B	27-12-95
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		NO 179674 B	19-08-96
		OA 9521 A	15-11-92
		WO 9013548 A	15-11-90
		US 5151423 A	29-09-92
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WO 9630363 A	03-10-96	AU 5307796 A	16-10-96
WO 9630018 A	03-10-96	AU 5189196 A	16-10-96
WO 9631478 A	10-10-96	AU 5527996 A	23-10-96